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AUREOMYCIN THERAPY IN THE PULMONARY INVOLVEMENT OF PANCREATIC FIBROSIS (MUCOVISCIDOSIS)*

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THIS report is concerned with aureomycin|| in the treatment of patients with pancreatic fibrosis (cystic fibrosis of the pancreas).[1-3] Numerous advances in the understanding of the nature of the disease, development of diagnostic procedures and clinical management have been made in a series of correlated studies carried out at the Boston Children's Hospital.[4-21] The common notion that this is a rare disease and that the immediate prognosis is always poor is no longer tenable. Another misconception, perhaps based on historical and nosologic grounds, is the view that this is a disease solely of the pancreas and that involvement of other organs, chiefly the lungs and liver, is secondary to the disorder in the pancreas. Farber[9, 17] described the generalized nature of this disease and has introduced the term "mucoviscidosis" to signify the essential alteration in mucus-secreting glands as a primary defect. There is sufficient clinical variation in the disease to indicate that different degrees of involvement in different organs exist. However, one is struck by the frequency of pulmonary symptoms early in the disease in the majority of patients. These symptoms are cough, often paroxysmal and at times suggestive of pertussis, or wheezing respirations with the production of thick, tenacious mucus. Atelectasis and emphysema with infection, primary or secondary, are the chief features as seen clinically and as demonstrated by roentgenograms. Indeed, the roentgenogram of the chest may be sufficiently characteristic to suggest the diagnosis of pancreatic insufficiency.[16] The respiratory rate may be increased, and the chest often becomes rounded, with increased anteroposterior diameter. Vital capacity and exercise tolerance are diminished. Clubbing of the fingers and cyanosis may follow. If the pulmonary lesion advances, irreversible changes such as bronchiectasis and multiple staphylococcal abscesses may develop. A constant feature is the laboratory finding of *Staphylococcus aureus* in the nasopharynx of these patients.

The management of a patient with this disease involves consideration of replacement therapy in the form of pancreatin, the use of protein hydrolysates, the administration of a high-calorie diet with some restriction of fat, and liberal supply of vitamins, including water-miscible vitamin A. The pulmonary infection is perhaps superimposed upon a more fundamental defect, as yet not fully understood, and its successful therapy is a problem of grave concern. The introduction of the sulfonamides, penicillin and streptomycin marked a signal advance in the management of the pulmonary infection. The use of aerosol therapy with penicillin or streptomycin, alternating with variable periods of oral sulfadiazine, has become part of routine management. This combined form of therapy under constant medical supervision has proved beneficial to most patients. The cost of the therapy outlined above is high. The administration of aerosol therapy to small infants is difficult, and even the older child is not always fully co-operative. The substitution of an orally effective antibiotic such as aureomycin for the expensive and more difficult form of aerosol therapy has obvious merits.

Aureomycin has been shown to have a wide range of activity against bacteria, rickettsia and certain viruses.[22-27] It has been found to be effective in vitro against the staphylococcus species isolated from patients with pancreatic fibrosis as determined

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||A generous supply of aureomycin for use in this study was furnished by the Lederle Laboratories, New York City.

in this laboratory. A modest amount of experience in the treatment of a variety of infections in children, including some caused by the staphylococcus species, indicated that a satisfactory response could be expected and that toxic effects would be minimal. The favorable clinical response to aureomycin of a three-year-old patient with pancreatic fibrosis and extensive pulmonary involvement indicated that further use of the drug was warranted.

Plan of Study

Early in the course of this study aureomycin was used only to replace aerosol therapy with penicillin or streptomycin, or both. However, as experience was gained the drug was administered more liberally, even to patients with minimal pulmonary signs, who at the time were not receiving antibiotic therapy. These patients were followed in the Nutritional Clinic on an outpatient status or as private patients and were seen by the same observers at intervals of two to five weeks. Many of the older patients have been followed for several years in the same clinic and their response to antibiotic therapy is well known. This background served as a basis for comparison, particularly when the only change in the plan of therapy was the substitution of aureomycin for other antibiotic agents. The same dietary schedule, including the use of pancreatin, was followed. In all the cases considered in this study the diagnosis was confirmed by duodenal-fluid assay for trypsin,* and in many cases corroborated by abnormal glycine absorption after an oral gelatin feeding[20] and by the failure to find trypsin in the stools.[21] A total of 35 patients have been treated and followed for at least a two-month period after the institution of aureomycin therapy. The longest period of observation extends over four and a half months. At least 15 additional patients could be included if the data were analyzed on a shorter observation period. In the latter group the response has been similar to that observed in patients followed over a longer time. Frequent laboratory observations were made including roentgenograms of the chest, white-cell counts and nose and throat cultures, the last being taken on each visit. The patients considered ranged in age from five weeks to twelve years.

Table 1. *In Vitro Aureomycin Sensitivity of Micro-organisms Isolated from Thirty-Two Miscellaneous Infections.*

Micro-organism	No. of Strains Tested	Aureomycin Sensitivity					
		Strains requiring more than 4.0 microgm./cc.	Strains requiring more than 2.5 microgm./cc.	Strains requiring more than 1.0 microgm./cc.	Strains requiring more than 0.5 microgm./cc.	Strains requiring more than 0.25 microgm./cc.	Strains requiring more than 0.064 microgm./cc.
Esch. coli	7	7	—	—	—	—	—
A. aerogenes	3	1	1*	—	1*	—	—
Ps. aeruginosa	9	9	—	—	—	—	—
H. influenzae	2	—	—	1	—	—	1
Staph. aureus	4	—	—	—	—	3	1
Pr. vulgaris	2	2	—	—	—	—	—
Neisseria catarrhalis	3	1	—	—	1	1	—
Beta streptococcus	1	1	—	—	—	—	—
Corynebacterium diphtheriae	1	1	—	—	—	—	—

*Type B.

Table 2. *In Vitro Sensitivity of* Staph. aureus *Isolated from Nasopharynx of 42 Patients with Pancreatic Fibrosis before Treatment with Aureomycin.*

Concentration of Drug* Required	Strains Sensitive to Aureomycin	Strains Sensitive to Streptomycin	Strains Sensitive to Penicillin
More than 4.0	5 (12%)	11 (44%)	19 (74%)
2.0	3	—	—
1.0	4	1	—
0.5	10	—	—
0.25	8	—	—
0.125	10	—	—
0.064	1	6	2
0.032	1	4	3
0.008	—	1	—
0.004	—	2	2
Totals	42	25	26

*For aureomycin, microgm. per cubic centimeter, for streptomycin, mg. per cubic centimeter, and for penicillin, Oxford units per cubic centimeter.

Dosage

Aureomycin is supplied in gelatin capsules, a form inconvenient to dispense to infants and young children. Inasmuch as the drug is unstable in solution,[28, 29] the capsule was opened, and the dried powder given with food or drink. The drug may be rejected because of its bitter taste.† However, most parents have succeeded in its administration. At first the drug was given four times a day, but more recently it has been given in divided or even in single daily doses. An effort has been made to provide the minimal effective amount for each patient. This is roughly 20 to 30 mg. per kilogram of body weight, or 125 to 250 mg. daily, in divided

*In 2 patients (Cases 9 and 35) duodenal intubation was not performed. However, the diagnosis was made on clinical grounds in addition to abnormal gelatin absorption and absent stool trypsin.

†Aureomycin-flavored powder (spersoids) has been employed in a small number of cases. with favorable results. This preparation, which can be added to milk or other fluids, overcomes the unpleasant taste.

or single doses for infants and 250 to 750 mg. per day in two or three divided doses for children.

Bacteriologic Studies

The flora of the upper respiratory tract was determined on each patient by separate nasopharyngeal and throat swabs taken before therapy and at each subsequent visit. The staphylococcus species isolated were studied for sensitivity to various antibiotics.

In vitro sensitivity to aureomycin was determined by a tube-titration method similar to that employed for penicillin sensitivity.[30] Aureomycin is diluted so that four times the desired concentration is contained in a volume of 0.5 cc. of tryptic digest broth and diluted serially by 50 per cent decrements. An eighteen-hour broth culture of the micro-organism to be tested is diluted 1:100, and 1.5 cc. of this dilution is added to each 0.5-cc. dose of aureomycin. The range of final concentrations usually employed is 4.0 to 0.004 microgm. per cubic centimeter. The tubes are incubated at 37°C. for sixteen hours. The last tube showing complete inhibition of growth is taken as the end point. Since aureomycin rapidly loses potency in solution the end points at sixteen hours may be higher than those at twelve hours. The composition of the medium also influences the rate of loss of aureomycin activity.[31] However, with standardized conditions the method outlined above checks within one tube in duplicate titrations. These determinations are considered to be of only relative value, inasmuch as an arbitrary concentration of 4.0 microgm. per cubic centimeter has been selected as an end point in this study. It should be emphasized that in no case has in vitro sensitivity influenced either the use or the dosage of the drug. Aureomycin blood and urine levels have not been undertaken in view of the difficulties inherent in such determinations.[32]

Table 1 summarizes the in vitro sensitivities of the micro-organisms isolated from 32 patients other than those with pancreatic fibrosis. *Haemophilus influenzae* and *Staph. aureus* were the most sensitive of the species included in this small series. It is interesting to note that all strains of *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus vulgaris* required more than 4.0 microgm. per cubic centimeter for inhibition, since it has been reported that aureomycin is relatively ineffective against *Ps. aeruginosa* and *Pr. vulgaris*.[29, 33] The greater resistance of these species is further reflected in their appearance or persistence in the nasopharynx of patients receiving aureomycin.

Table 3. *Response to Aureomycin Therapy.*

Case No.	Sex	Age at Appearance of First Pulmonary Symptoms	Age at Time of Diagnosis	Present Age	General Condition at Start of Therapy	Weight at Start of Therapy		Duration of Therapy	Clinical Response
		mo.	*mo.*	*mo.*		*lb.*	*oz.*	*wk.*	
1	M	½	1	2	Poor	6	3	4	Good*
2	F	1	4	6	Poor			7	Fair
3	F	2½	2	8	Patient acutely ill	8	6	10	Good
4	M	1¼	1	9	Fair	12	8	14	Excellent
5	F	¼	9	11	Poor	11	7	8	Excellent
6	M	1½	2½	13	Fair	16	3	12	Excellent
7	M	1¼	6	14	Poor	15	13	10	Excellent†
8	F	1	(3 days)	14	Good	19	0	7	Fair
9	M	5	5	17	Good	19	6	1	No change
10	M	1¼	4¼	17	Poor	20	2	16	Good
11	M	9	7	17	Poor	11	6	9	Excellent
12	F	1	3	19	Poor	20	9	16	Excellent
13	F	1	2	20	Very poor	16	6	9	Excellent
14	F	1½	1½	20	Very poor	23	0	12	Excellent
15	F	¼	16	20	Poor	20	2	8	Excellent
16	M	3	8	21	Fair	25	0	8	Excellent
17	F	½	16	22	Poor	16	2	11	Good
18	M	6	6	24	Patient severely ill	23	0	12	Excellent
19	M	18	25	26	Very poor	23	0	4	Excellent
20	F	2½	2	27	Poor	20	0	12	Excellent
21	F	20	25	28	Fair	22	15	8	Excellent
22	M	½	11	28	Poor	18	4	17	Excellent
23	F	3	11	31	Poor	24	4	15	Excellent‡
24	M	24	24	36	Good	26	0	9	Good
25	F	¼	8	44	Very poor	19	0	18	Excellent
26	M	2½	28	47	Fair	32	0	8	No change
27	M	4	5	53	Poor	33	8	12	Excellent
28	M	½	54	57	Fair	33	0	10	Excellent
29	F	4	15	65	Fair	35	4	8	Excellent
30	M	4	52	73	Poor	39	0	8	Excellent
31	M	34	40	79	Poor	27	0	9	Excellent
32	F	36	19	111	Fair	43	0	8	No change
33	M	90	66	115	Poor	41	0	11	Excellent*
34	F	72	94	117	Fair	49	4	16	Excellent
35	F	72	139	144	Grave	61	0	1½	No change

*Private patients of Dr. R. M. Smith.
†Rubeola developed 18 days after aureomycin was started.
‡Rubella developed 1½ mo. after aureomycin was started.

Results

In Vitro Studies

Table 2 presents a comparison of the in vitro aureomycin, penicillin[30] and streptomycin[34] sensitivities of the strains of *Staph. aureus* isolated

from the nose and throat cultures of cases of pancreatic fibrosis. Most of these patients had previously received penicillin or streptomycin, or both, but not aureomycin at the time these determinations were done. As may be seen in Table 2 only 12 per cent of the strains tested required a concentration of more than 4.0 microgm. per cubic centimeter of aureomycin for inhibition, as compared to 44 and 74 per cent requiring more than 4.0 mg. of streptomycin or 4.0 Oxford units of penicillin respectively. The number of strains resistant to penicillin and streptomycin in this series may be on aureomycin titrations done on a single fishing from each culture. However, in other cases, multiple fishings from the same culture yielded identical sensitivities when examined in the same manner. It seems unlikely that the increased resistance observed in these 7 patients was due to variations in the sensitivity of different fishings of the same strain, as has been true of streptomycin.[35]

Pulmonary Signs and Symptoms

The most striking effect of aureomycin therapy was the consistent amelioration of cough, dyspnea

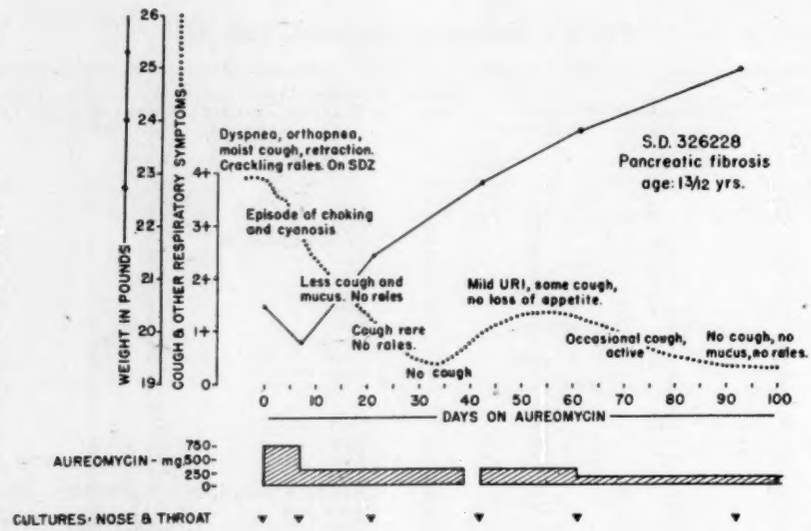

FIGURE 1. *Summary of the Effect of Aureomycin Therapy on the Course in Case 12. Note abatement of respiratory symptoms and marked weight gain.*

in part a reflection of previous exposure to these antibiotics. However, it has been observed in a large series of strains studied in this laboratory that *Staph. aureus* is frequently penicillin resistant and streptomycin sensitive, both before and after exposure to the antibiotics.[35]

The flora of the nose and throat was essentially unchanged in many patients after they had received aureomycin. Clinical improvement bore no relation to bacteriologic improvement, the former being commonly and the latter only rarely observed. When a staphylococcus species was isolated during the course of therapy, repeated in vitro sensitivity to aureomycin was determined. Such data were obtained on 18 patients. In 7 cases an increase in resistance ranging from fourfold to thirty-two-fold was observed. On the other hand there were only 2 cases in which repeat titrations failed to check within one tube. These observations were based and respiratory distress. Fever, if present, was likewise favorably affected. Response was rapid, a change usually occurring within two or three days. Cough, which often kept the child awake through the night or occasionally induced vomiting, either stopped abruptly or became minimal. In some cases the parents stated that for the first time in weeks the child slept through the night without cough. This excellent response was observed in 31 of the 35 patients (Table 3). Two patients (Cases 26 and 32) showed only minimal improvement, probably because of inadequate dosage. One child (Case 35), the oldest in the series, had extensive bilateral bronchiectasis of six years' duration and a ten-day course of drug had no noticeable effect. As would be expected the physical examination of the chest showed little or no alteration in the fixed hyperexpanded thorax. Auscultatory signs varied; in some cases there was complete disap-

pearance of rales and rhonchi, and in others these signs persisted. In a few patients with bronchiectasis, clinical improvement appeared without any significant change in the physical findings in the chest.

General Condition

Improvement in disposition and well-being often accompanied the relief of respiratory symptoms. Two of the older boys felt so well that for the first time they were able to compete in the vigorous activities enjoyed by their playmates. In addition, a striking improvement in appetite was noted in many patients. This is of interest in view of the voracious appetites many of these patients possessed before pulmonary infection supervened. Weight gain was noted frequently and was striking in some patients (Fig. 1).

Effect on the Stools

The action of aureomycin on the gastrointestinal tract deserves special attention. Nausea and vomiting are mentioned as frequent side effects in the adult. These symptoms were rarely encountered in this series of patients. The stools increased in number and became loose in the majority and watery in a few cases. The offensive odor commonly associated with the stools of these patients became less noticeable. The stools took on a yellowish or greenish color. There appears to be a rough relation between dosage and bowel activity. In the infant age group 500 mg. or more a day may produce a troublesome diarrhea. This is likely to stop after twenty-four to forty-eight hours off the drug. In 1 patient (Case 9) the drug had to be discontinued after three separate trials, because of severe diarrhea even on minimal dosage. It should be noted that some of the most encouraging gains in weight were observed in patients who had diarrhea. In patients other than those with pancreatic fibrosis who were treated with aureomycin in the same dosage schedule diarrhea did not develop.

The effect of aureomycin on the aerobic bacterial flora of the stool has been studied in a small series of cases. The results varied from no effect in most cases to complete disappearance of the normal flora while the patient was receiving therapy. In several cases the persistence or appearance of *Ps. aeruginosa* or *Pr. vulgaris* was observed in the stool after the disappearance of the usual aerobic flora.

Stool Trypsin

The absence of tryptic activity in the stool is unaltered by this drug in patients receiving inadequate or no pancreatin therapy. On adequate pancreatin therapy stool trypsin is regularly demonstrated regardless of whether or not the patient is receiving aureomycin.

White-Cell Count

The white-cell count does not necessarily reflect the activity of the pulmonary infection. Except during acute episodes this measurement is not very useful. In some cases the elevated count returned to normal levels after aureomycin therapy, but this was not a constant observation.

Roentgenograms

In most cases roentgenograms were taken previous to aureomycin therapy and at frequent intervals thereafter. Some improvement was seen, but this was not comparable to the excellent clinical response (Fig. 2).

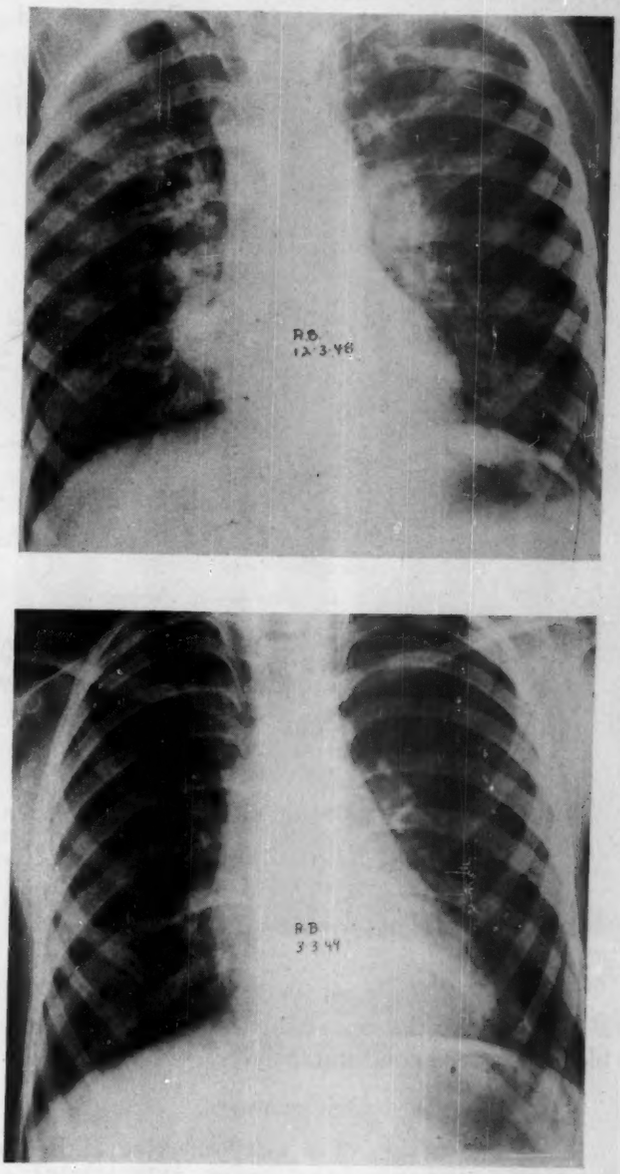

FIGURE 2. *Roentgenograms of the Chest in Case 28 Taken before Aureomycin Was Started (Upper Film) and Three Months Later (Lower Film), Showing Improvement in the Extent of the Pulmonary Involvement.*

The Problem of Relapse

Aureomycin was discontinued in several patients after varying periods. Within three to seven days a relapse occurred, particularly in those with ex-

tensive pulmonary involvement. Readministration of the drug resulted in improvement. No refractoriness to the drug developed in this short period of observation.

Data from 2 patients are presented in Figures 2 and 3 to illustrate the nature of the response to aureomycin and to emphasize many of the statements made above. These figures are self-explanatory. In addition a summary of the treated cases arranged according to age of patient is presented in Table 3.

Figure 4 demonstrates the appearance of a patient (Case 19) taken before and after four weeks of aureomycin therapy with a dose of 125 mg. twice a day. As in the remaining cases no other antibiotic was used concomitantly.

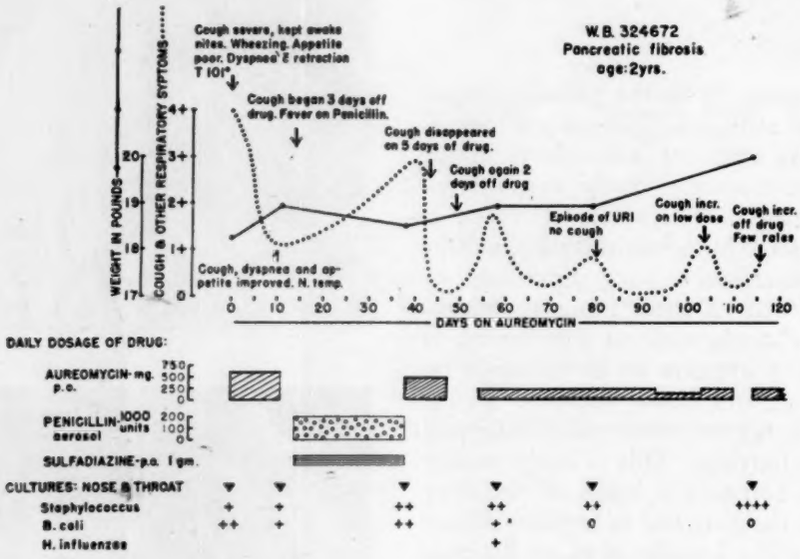
W.B. 324672
Pancreatic fibrosis
age: 2yrs.
Cough severe, kept awake nites. Wheezing. Appetite poor. Dyspnea & retraction T 101°
Cough began 3 days off drug. Fever on Penicillin.
Cough disappeared on 5 days of drug.
Cough again 2 days off drug
Episode of URI no cough
Cough incr. on low dose
Cough incr. off drug Few rales
Cough, dyspnea and appetite improved. N. temp.
WEIGHT IN POUNDS
COUGH & OTHER RESPIRATORY SYPTOMS
DAYS ON AUREOMYCIN
DAILY DOSAGE OF DRUG:
AUREOMYCIN-mg. p.o.
PENICILLIN-1000 units aerosol
SULFADIAZINE-p.o. 1 gm.
CULTURES: NOSE & THROAT
Staphylococcus
B. coli
H. influenzae

FIGURE 3. *Summary of the Course in Case 22 during the Period of This Study. Note that although penicillin aerosol and sulfadiazine did not control the respiratory symptoms, aureomycin repeatedly resulted in improvement in cough.*
It should also be noted that cessation of the drug or inadequate dosage caused a recurrence of symptoms.

Discussion

The introduction of a new, effective antibiotic in the management of patients with the pulmonary complications of pancreatic fibrosis simplifies the present mode of therapy. Inasmuch as the drug is effective in small oral doses and possesses few undesirable properties, it may become a most useful adjunct to the other therapeutic agents used in the treatment of this condition. The prompt return of symptoms when the drug is discontinued should be emphasized. That such an agent will be most effective when administered early in the course of the pulmonary disease is obvious. It is equally clear that the drug will be of little ultimate value in advanced bronchiectasis. Prophylactic administration of aureomycin to small infants with pancreatic fibrosis to delay or prevent the appearance of pulmonary infection appears to be rational. It may likewise prove worth while to follow carefully the siblings of patients with known pancreatic fibrosis and babies with meconium ileus so that prophylactic aureomycin therapy can be instituted when indicated. That the drug can be given continuously over a long period without untoward effect has been demonstrated.

Although aureomycin is presumably effective because of its antibacterial properties, the persistence of the same bacterial flora in the nasopharynx despite the marked clinical improvement observed in the majority of patients suggests the possibility of other effects in pancreatic fibrosis. Perhaps the effectiveness of aureomycin in pancreatic fibrosis is due to bacteriostatic rather than bactericidal activity, because of the presumably low in vivo concentrations obtained with the dosage schedules employed. Prolonged bacteriostasis, even though not lethal for the bacterial cell, may induce physiologic changes resulting in profound metabolic alterations, mutations or loss of virulence. In any event it is apparent that bactericidal activity is not essential to clinical improvement in pancreatic fibrosis. This behavior may also explain the rapidity of relapse with removal of the drug.

The development of bacterial resistance to aureomycin has not yet been definitely established, although observations on 7 of the patients in this series suggest that resistance can be acquired after

in vivo exposure. However, these patients continued to show clinical improvement on the same dosage schedule despite increasing in vitro resistance.

The appearance of *Pr. vulgaris*, *Ps. aeruginosa* and fungi in the nasopharynx of patients treated with aureomycin, overgrowing or replacing the initial bacterial flora, is reminiscent of similar phenomena that have been observed repeatedly during prolonged penicillin or streptomycin therapy.

of cough, improved general well-being, increased appetite and weight gain. An increase in the number and looseness of stools was noted in most patients. The drug had to be discontinued in 1 patient because of severe diarrhea. No other untoward effects were encountered. The discontinuance of the drug resulted in the prompt reappearance of symptoms.

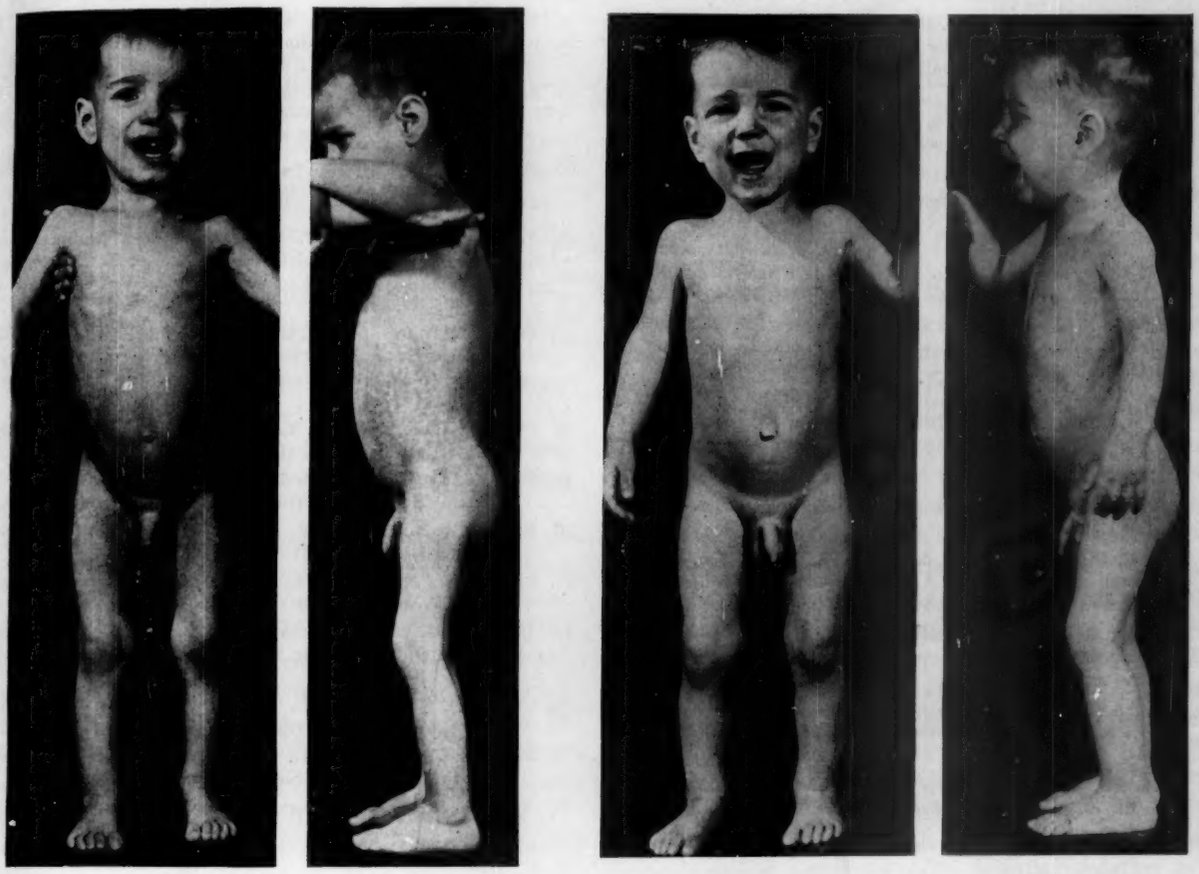

FIGURE 4. *Photographs of Patient in Case 19 Taken at the Start of Aureomycin Therapy (Left), and after Four Weeks of 125 mg. Twice Daily (Right).*
Note the improvement in nutrition and general appearance. The patient gained 4 pounds in four weeks.

SUMMARY

Aureomycin is effective in the management of the pulmonary involvement in pancreatic fibrosis.

Thirty-five patients treated with different oral doses were followed for periods varying up to four and a half months. The minimal effective dose ranged from 20 to 30 mg. per kilogram of body weight given in one or two divided doses a day.

The response was good to excellent in 31 of the 35 cases. This was characterized by disappearance of cough, improved general well-being, increased appetite and weight gain. An increase in the number and looseness of stools was noted in most patients. The drug had to be discontinued in 1 patient because of severe diarrhea. No other untoward effects were encountered. The discontinuance of the drug resulted in the prompt reappearance of symptoms.

Staphylococcus aureus was isolated from the nasopharynx of all patients included in this series. The clinical improvement was independent of the bacteriologic findings as determined by study of the nasopharyngeal flora. The in vitro sensitivity of the *Staph. aureus* isolated from these patients was determined for penicillin, streptomycin and aureomycin. The majority of strains were relatively more sensitive to aureomycin than to either of the other two antibiotics. The *Staph. aureus* isolated from 7 patients during aureomycin therapy showed an apparent increase in resistance ranging from fourfold to thirty-two-fold.

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POSTERIOR TUBERCULOUS SINUSES OF VERTEBRAL ORIGIN*

Wound Revision and Closure with Streptomycin Permitting Early Spinal Fusion

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BEFORE the advent of streptomycin, half the patients having sinuses associated with Pott's disease died. Many procedures were devised and advocated for the control of tuberculous abscesses and sinuses but were uniformly characterized by poor therapeutic response. Aspiration of abscesses and excision of sinuses were followed by recurrence in about 60 per cent of the cases.[1-9] When such foci of soft-tissue infection presented near the site of tuberculous spondylitis, it was rarely possible to perform spinal fusion without considerable risk to the patient. Usually, in the face of this common complication, all thought of spinal fusion was abandoned. The only alternative was a prolonged and uncertain program of rigid immobilization, the patient being subjected to a variety of physical and chemical agents in an effort to control the tuberculous sinus.

Developments of recent years have greatly improved the outlook of the patient with tuberculous spondylitis. Spinal fusion continues to be the most effective method for control of the vertebral infection, but streptomycin therapy has proved extremely important in the control of the frequently associated infection of soft tissues.[10-14] We are concerned in this study with the posterior tuberculous abscess or sinus complicating Pott's disease, which interferes, by threat of contamination, with the early, definitive care of the underlying vertebral disease. Prompt and effective relief of such posterior foci permits fusion of the spine and rehabilitation of the patient in a period often measured in terms of months, rather than years.

Streptomycin will heal most tuberculous sinuses without adjunctive surgical measures, unless drug fastness has developed. However, such treatment is usually prolonged. Twelve of 15 sinuses in Hinshaw's[10] series closed without recurrence, but the duration of treatment recommended was three to four months.

When Brock[11] used streptomycin and adequate drainage, 59 of 60 sinuses closed. Seventy per cent of these sinuses required ten to twenty weeks of drug administration to heal. In our clinic this regime was followed with similar results, but we have found that the period required for healing by second intention with streptomycin may be reduced by surgical closure after adequate wound revision. Our results on secondary and primary closure of the excised tuberculous abscess or sinus with streptomycin therapy have been reported elsewhere.[14]

Since our previous report we have confirmed the value of this mode of management, and a much larger series of cases is available for clinical evaluation. In 2 out of 7 cases in which wound revision and primary closure was undertaken, reformation of an abscess under the firmly healed wound occurred. When a period of continuous decompression following débridement was allowed (from two to six weeks) before wound closure was undertaken, only 2 out of 26 cases presented recurrence of a sinus in the healed revision wound. One of these closed before completion of the first course of streptomycin, whereas the other, which was more profusely draining, closed during a second course of streptomycin given for another indication. Both have remained firmly healed. Thus, delayed closure is found, in general, to be the more effective procedure. The chronic, meagerly draining sinus, small in total extent, may be closed by excision and primary suture. When rapid reaccumulation of pus or excessive drainage presents clinically, adequate débridement and a period of continuous decompression are necessary before revision and secondary closure of the wound.

The effectiveness of streptomycin in the treatment of tuberculous sinuses has been improved by the observation of certain surgical principles. These principles are as follows: *superficial encapsulated tuberculous pus must be adequately drained; the tuberculous sinus must be widely deroofed; tuberculous granulation and fibrous tissue must be removed; and extravertebral necrotic bone and cartilage must be removed.*

GENERAL INDICATIONS FOR STREPTOMYCIN THERAPY

Management of the posterior tuberculous abscess or sinus by surgical measures and adjunctive streptomycin therapy varies according to the nature and location of the process. Several categories are met with, two or more of which frequently coexist in the same patient. Some of these abscesses and sinuses should be disregarded when spinal fusion is undertaken. Others require a staged surgical

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program geared to the effective zone of streptomycin therapy. It should be emphasized that the goal is the early fusion of a tuberculous spine.

The paravertebral tuberculous abscess under the anterior longitudinal ligament offers no contraindication to spinal fusion, nor does it of itself constitute an indication for streptomycin therapy except when spinal-cord compression complicates the problem. The tuberculous paravertebral mass frequently decreased in size under streptomycin therapy (Cases 3 and 4), so that streptomycin is indicated when signs of spinal-cord compression exist. Conversely, absence of clinical response to an initial course of streptomycin in the presence of a highly suspicious vertebral lesion and paravertebral mass, with signs of spinal-cord compression, suggests a nontuberculous etiology.* Less serious pressure manifestations of the space-occupying mass are easily relieved by repeated aspirations, without the use of streptomycin, until fusion is completed. Because of the prolonged drainage that follows costotransversectomy, even under months of streptomycin therapy in 2-gm. daily doses,[15] this procedure should be delayed, if possible, until the spinal fusion is completed (as in Case 5).

The deep, burrowing extension abscess (psoas and so forth) and its more superficial sequelae, which do not point or drain posteriorly, offer no contraindication to spinal fusion. This applies only so far as these infected zones do not present in the projected area of spinal fusion and are, therefore, no hazard from the standpoint of wound contamination.

The posterior tuberculous sinus and the subcutaneous abscess with marked thinning of the skin, close to the proposed operative area, have been established as contraindications to spinal fusion. When the tuberculous sinus is the entire and major problem, its management by secondary healing or surgical closure under streptomycin is elective. However, when the sinus is associated with Pott's disease and its proximity contraindicates required spinal fusion, indefinite delay of fusion is avoided by surgical closure of the sinus under streptomycin therapy. The major surgical procedure can then be performed in the safest zone of streptomycin therapy.

Case Reports

This study includes 6 cases of tuberculous spondylitis in which spinal fusion was desirable. In each of these patients fusion was contraindicated by posterior, superficial tuberculous abscesses or sinuses immediately adjacent to the operative field. Two of the foci treated were situated in the posterior midline and the remaining sites ranged from 3 to 12 cm. from the midline, with an average distance of 4 cm.

*G. E. W., Jr. (R.H.V.A.H. 20,430), a 25-year-old man with progressing paraplegia associated with collapse of the tenth dorsal vertebra and a small paravertebral mass, was transferred to this hospital with a diagnosis of tuberculous spondylitis after having been in two teaching hospitals. Two diagnostic aspirations of the mass yielded only blood. There was no clinical response to a 3-gm. course of streptomycin. Laminectomy decompression was then performed, and biopsy of the involved vertebra revealed a primary, malignant capillary hemangioendothelioma.

Case 1. J. W. M. (R.H.V.A.H. 19,208), a 28-year-old man, was admitted to the hospital on June 20, 1946, with a diagnosis of bilateral pulmonary tuberculosis, moderately advanced.

A roentgenogram of the chest revealed bilateral apical infiltrations. The sputum was normal. Serial films showed progressive clearing and contraction of the apical disease during the next 3 months. In September the patient complained of pain in the right hip. Roentgenograms of the right hip were normal but the lumbar spine showed decalcification and erosion of the anterior surface of the body of the first and the upper border of the second lumbar vertebra, with irregularity and thinning of the intervertebral disk. A presumptive diagnosis of tuberculous spondylitis was made, and the patient was treated by bed rest and Taylor back brace.

In January, 1947, roentgenograms of the spine showed increased destruction of the first and second lumbar vertebras and beginning involvement of the twelfth thoracic vertebra. The right psoas shadow was obliterated by a mass, presumably a psoas abscess. A 4-cm. mass could be palpated in the right lumbar region. The mass rapidly increased to about 15 cm. in diameter, undermined across the midline, and pointed above the right iliac crest. It was acutely tender. Frequent aspirations yielded tuberculous pus, and two draining sinuses developed.

On March 4 intramuscular injection of streptomycin was begun, the dosage being 2.0 gm. a day. On the following day the right-psoas-muscle abscess was drained, and 1200 cc. of green, creamy pus was recovered. The abscess occupied a space between the peritoneum and the lumbodorsal fascia, extending from the right tenth rib into the true pelvis. It had dissected to the left paravertebral region, superficially through Petit's triangle, and had undermined to the right anterior superior iliac spine. The right quadratus lumborum and psoas muscles were almost totally destroyed. A counter-incision was used to drain a daughter abscess over the right posterior superior iliac spine.

During the next 2 months the small daughter abscess and its sinus tract closed, and the superficial undermining area across the midline healed solidly. On May 10, a 12-day course of penicillin was started, consisting of 300,000 units a day. Six days later the wound was revised, the sinus tract and abscess being partially excised, and was closed without drainage. Five weeks later a Hibbs spinal fusion was done from the tenth thoracic to the fourth lumbar vertebra. The fusion mass was supplemented by bone chips taken from the left ilium. Streptomycin was discontinued on July 22, after 140 days of administration. The secondarily closed sinus and the spinal fusion incision have remained solidly healed. The patient was discharged in December and has remained well during the 20 months since his last operation.

Case 2. W. J. M. (R.H.V.A.H. 19,385), a 22-year-old man, was admitted to the hospital on September 11, 1946, with a diagnosis of Pott's disease of the fourth and fifth lumbar vertebras, and left psoas abscess.

A roentgenogram of the chest revealed bilateral apical infiltration. The sputum was normal. Roentgenograms of the spine showed degenerative changes of the fourth and fifth lumbar vertebras and a left paravertebral mass. A fluctuant, nontender, slightly warm mass, measuring 15 by 5 cm., was felt in the left lumbar region. This mass was centered over the left iliac crest and extended medially across the lumbar spine. The skin overlying the paraspinal region of the mass was thin.

On October 9 a diagnostic aspiration of the left psoas abscess was performed, after which the abscess ruptured spontaneously and began to drain thick, caseous tuberculous pus. Iodized oil injected into the sinus revealed a tract directed anteromedially, not quite reaching the fourth lumbar interspace.

On March 4, 1947, intramuscular injection of streptomycin, 2.0 gm. daily, was begun. On the following day, débridement of the sinus was performed, and considerable diseased tissue was removed. The wound was packed loosely with iodoform gauze.

On June 13 a 10-day course of penicillin was started, consisting of 300,000 units a day. Six days later wound revision and secondary closure was performed. The sinus tract was removed surgically as far as the transverse process of the fourth lumbar vertebra. The fascial layers were developed and sutured without drainage. The wound healed firmly. On July 12 streptomycin was discontinued. A two-stage Hibbs spinal fusion was performed on August 27 and October 8. Convalescence was uneventful. The patient was discharged on March 25, 1948, and has remained well during the 17 months since the final operation.

Case 3. H. W. K. (R.H.V.A.H. 19,758), a 32-year-old man, was admitted to the hospital on December 23, 1946, with a tuberculous sinus in the left posterior lumbar region. The eleventh and twelfth dorsal vertebras showed demineralization, but the intervening disk was not thin. In addition there was a left tuberculous pleural effusion, and an apparently arrested, minimal lesion in the upper lobe of the right lung. On October 21, 1945, a left lumbar abscess had been drained. Smear, culture and guinea-pig inoculation were all positive for tubercle bacilli. The vertebral lesion had been diagnosed as tuberculous spondylitis, and a Bradford frame had been employed since December 13, 1945.

Lipiodol studies demonstrated that the sinus extended to the level of the disk between the eleventh and twelfth dorsal vertebras, where it angulated forward to end in a small pocket. On March 14, 1947, chest x-ray study disclosed a diffuse haze through all lobes of the lungs, highly suggestive of miliary tuberculosis. By March 28, these granular markings had increased considerably, and streptomycin, 2.0 gm. a day, was begun. The clinical response was excellent, and radiologic clearing was demonstrated by serial chest films. Spinal fusion was then considered in an effort to utilize the favorable streptomycin response.

On July 15 the sinus tract was thoroughly debrided, revised and closed primarily without drainage. There had been no decrease in size of the sinus under streptomycin, but the amount of drainage had diminished considerably in recent weeks. Firm wound healing occurred by first intention. The course of streptomycin ended on July 27. The vertebral bodies of the eleventh and twelfth dorsal vertebras had become more calcified, with considerable restoration of normal trabecular markings. Some anterior bone bridging was noted, and the paravertebral mass had decreased in size.

On August 13, the patient complained of malaise, nausea and headache. Lumbar puncture revealed an elevated spinal-fluid pressure, with 80 cells, predominantly lymphocytes, per cubic millimeter, a protein of 100 mg. per 100 cc. and low sugar and chloride values. The fluid was positive for tubercle bacilli on smear of the pellicle and by culture and guinea-pig inoculation. The patient was transferred to the medical service, where a second course of streptomycin, intramuscularly and intrathecally, was begun. He responded well for 3 weeks but then began to fail. Spinal-fluid streptomycin levels ranged from 15 to 194 microgm. per cubic centimeter. He died on November 23, 1947. The spinal-fluid organisms had become resistant to over 1000 microgm. of streptomycin per cubic centimeter.

At autopsy, the entire healed tract was carefully excised and studied. It included skin and the portion of the anterior vertebral ligament at the bone bridge. Many sections were studied by our consultant pathologist, Dr. Raymond Goodale, and sections were sent to the Army Institute for special investigation. Both reports stated that there was no evidence of tuberculosis.

Case 4. H. G. S. (R.H.V.A.H. 19,735), a 30-year-old man, was admitted to the hospital on April 3, 1947, for streptomycin therapy. He had had pulmonary tuberculosis since June, 1945, and a left artificial pneumothorax had been maintained since October, 1945. Tuberculosis of the left ninth rib had been diagnosed in July, 1946. Tuberculosis of the tenth and eleventh thoracic vertebras, with a right lumbar abscess, was discovered in September, 1946, In February, 1947, a spinal fusion was performed, tibial grafts with nut-and-bolt fixation being used. Several weeks after operation the wound broke down, and a soft mass appeared over the left iliac region. On admission the upper half of the dorsal spinal-fusion wound was separated and undermined, draining a moderate amount of tuberculous pus. There were rapidly reaccumulating, bilateral lumbar abscesses, which undermined the full thickness of the skin across the back.

X-ray study of the chest on admission showed a left pneumothorax and a pleural haze over the apex of the upper lobe of the right lung. Spinal films disclosed narrowing and irregularity of the disk between the tenth and eleventh dorsal vertebras; the body of the former was irregularly mottled. There was a 12.5-cm., dense, intact bone graft to the left of the spinous processes of the eighth to twelfth dorsal vertebras, and to the right there were two graft fragments secured by nut-and-bolt fixation. The right psoas shadow was not seen. There was an area of cyst-like rarefaction lateral to the upper angle of the left sacroiliac joint.

Drainage of the wound became slight, but smears and cultures of the wound and the lumbar abscesses were positive for acid-fast bacilli. No connection could be demonstrated between the wound and the lower lumbar abscesses. A 60-day course of streptomycin, 1.0 gm. a day, was begun on May 14. Two days later the wound was explored, excised and extended. The nut and bolt were easily movable, and the right-caudal-graft fragment was loose and roughened. These were removed. The wound was closed without drainage and healed by first intention. On May 26 the right psoas abscess was widely drained, and the undermining, symmetric lumbar collections of pus were counterdrained dependently. In all, over 1500 cc. of pus was removed. Revision and secondary closure was performed on June 18. All wounds remained firmly healed.

On August 12 films of the spine showed less mottling and some recalcification of the tenth dorsal vertebra. The paravertebral bulge was considerably less marked. The bone cyst in the left ilium was unchanged. The patient became ambulatory in a Taylor back brace.

On October 25, splenectomy was performed for acute, severe, idiopathic thrombocytopenic purpura. The patient died thirty-six hours postoperatively with a platelet-count rise to only 28,000. No accessory spleen was noted at operation. Permission for autopsy was not granted.

Case 5. A. R. (R.H.V.A.H. 20,133), a 30-year-old man with tuberculous spondylitis of the seventh, eighth and ninth thoracic vertebras had had a spinal fusion of the sixth to tenth dorsal vertebras performed in another hospital in June, 1944. He was discharged in January, 1945. He was next hospitalized in October, 1947, for a large fluctuant mass in the right costovertebral region. This mass was drained, and 800 cc. of tuberculous pus was recovered.

In November the patient was transferred to this hospital. He was seriously ill and had suffered a recent 15-lb. weight loss. Spinal roentgenograms showed extension of the disease above and below the fusion area and a large paravertebral mass in the posterior mediastinal compartment. Exploration of the fused area and extension of the spinal fusion were contraindicated by the presence of the nearby draining sinus.

Streptomycin, 1.0 gm. a day, was started on December 15, and the sinus was debrided and the abscess deroofed. Three weeks later the wound was revised and secondarily closed. On February 11, 1948, the fusion wound was explored, and a caudal extension of fusion from the eleventh dorsal to the twelfth lumbar vertebra was performed. There was no pseudarthrosis. Immediately after operation the patient became markedly depressed and unco-operative, vehemently resisting food and attempts at intravenous and gavage therapy. The fusion wound dehisced on the 14th postoperative day, and the sinus wound opened and began to drain 5 days later. Cultures were negative for pyogens and tubercle bacilli. With recovery of his mental status and under vigorous nutritional replacement therapy, the wounds healed rapidly. Pressure symptoms from his large paravertebral mediastinal mass became severe, requiring frequent aspirations. Streptomycin was discontinued on April 3.

On June 29, both twelfth ribs were removed because of tuberculous involvement. On September 15 the fusion was extended upward from the sixth to the fourth dorsal vertebra and a second course of streptomycin, 1.0 gm. a day, for 42 days was initiated. With the fusion completed and because of an increase in the width of the paravertebral

mass, a right costotransversectomy through the ninth and tenth ribs was done on November 15, draining the mediastinal abscess, with marked symptomatic relief. The patient became ambulatory on November 23. Both fusion wounds have remained firmly healed, and the mediastinotomy drainage has gradually diminished.

Case 6. J. L. D. (R.H.V.A.H. 18,749), a 23-year-old man, was first hospitalized in January, 1945. A right artificial pneumothorax was attempted for active pulmonary tuberculosis. It was abandoned in May because of adhesions, and in July of that year the right phrenic nerve was crushed and artificial pneumoperitoneum begun.

He was transferred to this hospital on November 25. X-ray films of the chest revealed fibrosis and mottled infiltrations throughout all lobes of both lungs, with honeycombing in the upper lobe of the right lung. Examination of the sputum was negative on admission but became positive in May, 1946. A left pneumothorax was induced on July 1, and was satisfactory.

The first major surgical procedure performed on this patient was a right extrapleural pneumothorax on July 29, 1947, under streptomycin protection, 1.0 gm. a day for 42 days. Three months later a right lumbar abscess developed. Repeated aspirations were negative for pyogens, fungi and acid-fast bacilli. The vertebral origin of this abscess could not be ascertained. Because of sinus-tract formation, a wide operative drainage was done on November 13. The right transverse processes of the lower lumbar vertebras were found to be bare and spongy. Biopsy of the abscess wall showed tuberculosis.

By April 8, 1948, serial x-ray films revealed that the disk between the sixth lumbar and the first sacral vertebra was thin and showed erosion of the anterior inferior border of the sixth lumbar vertebra. A left anterior suprainguinal abscess formed, draining spontaneously after repeated aspirations but yielding negative cultures.

On April 15 the second course of streptomycin, 1.0 gm. daily for 42 days, was begun. On April 21, secondary closure of the right posterior sinus was performed. The wound healed firmly. The anterior sinus offered no hazard of wound contamination to spinal fusion and was therefore disregarded. It healed spontaneously 20 days after completion of the second course of streptomycin. A Hibbs fusion of the fourth, fifth and sixth lumbar to first sacral vertebra was performed on May 12. Convalescence was uneventful. The patient became ambulatory with a Taylor back brace on August 11. He is asymptomatic, with a stable fusion, firmly healed wounds, right extrapleural pneumothorax, left intrapleural pneumothorax and a normal sputum since February 10.

General Procedure

Bacteriologic and anatomic studies must precede streptomycin therapy in the surgical treatment of tuberculous abscesses and sinuses. The tuberculous nature of an abscess or sinus is established by diagnostic smear and culture, guinea-pig inoculation or biopsy. It should be stressed that an adequate specimen must be sent to the bacteriologist. Streptomycin-sensitivity studies are carried out. Radiopaque oil is frequently helpful in outlining the extent of the pathologic process.

The optimal conditions for wound healing are obtained by adequate hydration, high-protein and high-caloric diet, supplementary vitamins and the correction of anemia.

Streptomycin, 0.5 gm. twice a day, and penicillin, 300,000 units daily, are given intramuscularly. Within three to seven days, the initial operation is conducted under general anesthesia. If the process is an *abscess*, it is incised and drained dependently. If the process is a *sinus*, its ramifications are deroofed. In either event, the tuberculous granulation and fibrous tissue is removed. Localized pockets of purulent material are counterdrained if necessary. The open wound is packed loosely with iodoform gauze. The pack is removed in forty-eight hours and replaced by saline dressings. These dressings are changed daily, and the wound is irrigated.

Seven days after the first operation, the wound is revised and secondarily closed. The basic surgical routine is as follows: under general anesthesia, the skin margins are cut a few millimeters from the edge of the wound. The sinus wall is excised. The wound is thoroughly lavaged with saline. After a change of instruments, drapes, gowns and gloves, the fascial planes and subcutaneous tissues are developed into layers and closed with interrupted sutures of fine chromic catgut. An attempt is made to obliterate dead space. The skin is closed with fine-silk sutures without drainage. A pressure dressing is applied. Streptomycin is given until healing of the sinus appears complete.

Inasmuch as organism resistance is in direct proportion to the amount of streptomycin used, every effort should be made to keep the total dosage at a minimum. In the special problem of posterior tuberculous sinuses the optimum dosage of 1.0 gm. of streptomycin daily may be reserved for the immediate operative period when closure of the sinus is accomplished. To protect the healed, surgically closed sinus wound, streptomycin should be continued at a reduced dosage schedule, until spinal fusion is performed, usually an interval of two or three weeks. The minimal safe but effective dose of streptomycin in this interval has not been established and probably varies with the activity of the underlying osseous lesion. Our present trend is toward the use of 1.0 gm. of streptomycin every second or third day.

Discussion

Posterior tuberculous sinuses associated with tuberculosis of the spine may present a specific problem. Spinal fusion frequently is not performed because of the presence of these superficial abscesses and sinuses in the projected operative area. Even with streptomycin and adequate drainage, spinal fusion is delayed because of the time required for healing by secondary intention. In addition, prolonged administration of streptomycin may be accompanied by drug toxicity and bacillary resistance.

Streptomycin is effective in the treatment of the early acute exudative lesion of tuberculosis caused by a sensitive organism, and hence is of value in operative procedures in which tuberculous dissemination may occur.[16] Streptomycin resistance of tubercle bacilli occurs initially in a few untreated cases, and as early as the fourth week in organisms initially sensitive to (inhibited by) 0.5 microgm. of streptomycin per cubic centimeter. Resistance is proportional to the total accumulated dose. It

may occur with astonishing suddenness and is probably irreversible. We do not yet have statistically significant figures on resistance studies in patients exhibiting active involvement of several bodily systems, such as pulmonary, skeletal and genitourinary, who have received streptomycin therapy. Until such data are available, the emergence of resistant organisms from any source in a given patient must be presumed to mean that similar resistance does, or will before long, exist in organisms in other foci within the same person.[17] Tuberculosis is a notoriously recurring disease involving many systems of the body. In the majority of cases, a brief course of streptomycin (measured in total grams) leaves one with a still potent agent for the treatment of unlooked-for complications in the same system, or subsequently arising in other systems.

In an attempt to overcome these problems we have added wound revision and primary or secondary closure of the sinus to obtain a clean operative field through which early spinal fusion can be performed. Internal immobilization of the tuberculous vertebras is accomplished with minimal delay and early in the course of streptomycin therapy. This immobilization will also accelerate healing of the secondary soft-tissue tuberculosis and probably reduce the incidence of sinus recurrence. Furthermore, preliminary study of nonorthopedic tuberculous sinuses suggests that surgical closure reduces the amount of streptomycin required for healing. With primary and secondary surgical closure of tuberculous sinuses, as little as five weeks of streptomycin therapy has sufficed.[14]

Recurrence of the sinus in some cases is likely and is an indication of continued activity of the tuberculous infection. In such cases a more intensive course of streptomycin may be required, but clinical judgment should be exercised if the presence of tuberculosis in extraskeletal systems presents other potentially major surgical problems. Maintaining a streptomycin-sensitive organism would then outweigh in importance the recurrence of a tuberculous sinus, particularly if the orthopedic operative problem had been solved. A patient now under observation illustrates this problem. Spinal fusion was performed in 1946 without the use of streptomycin therapy. In mid-1948 a tuberculous lumbar abscess, which drained spontaneously, developed. Roentgenographic examination showed the vertebral lesion to be in a healing phase. There was no extension of disease, and the fusion appeared solid. Observation over a period of months should enable us to decide whether or not further fusion is indicated. Until such a decision is made streptomycin will be withheld, and no surgical treatment of the sinus will be undertaken. If the sinus proves to be the entire problem, it can be readily managed as outlined above.

The ideal management of the problems presented in this study is often not possible. Long courses of streptomycin were given in the earlier cases because of inexperience, and in the later cases because we had extended our indications for spinal fusion. The experience gained has served to focus our attention more firmly on the conservation of streptomycin through judicious application of cardinal surgical principles initiated at the optimum time. In the favorable case, a short course of streptomycin may well result in a firmly healed posterior tuberculous sinus and fusion wound. In the unfavorable case the indications for spinal fusion may be extended.

Summary

A plan of management for the posterior tuberculous sinus of vertebral origin is described. Streptomycin is employed in a minimal total dosage through the application of established surgical principles, permitting spinal fusion to be performed early, in the safest zone of streptomycin treatment.

In the good-risk patient with a meagerly draining posterior sinus, excision and immediate closure under streptomycin protection result in a firmly healed wound. Spinal fusion may then be carried out early without danger of wound contamination.

In the good-risk patient with a copiously draining posterior sinus, adequate debridement and continuous decompression over a period of days are necessary. Subsequent wound revision and secondary closure under streptomycin therapy result in a firmly healed wound. Spinal fusion is thus but slightly delayed.

In the poor-risk patient with a posterior tuberculous sinus of vertebral origin, the unrestricted use of streptomycin may be necessary, but the plan of management permits spinal fusion early in the course of streptomycin therapy.

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PROGRESSIVE PRIMARY TUBERCULOSIS IN THE ADULT AND ITS DIFFERENTIATION FROM LYMPHOMAS AND MYCOTIC INFECTIONS*

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THE death rate from tuberculosis in the United States has decreased from 200 per 100,000 in 1900 to approximately 30 in 1948. The present population is intermittently rather than constantly exposed to tubercle bacilli; consequently, an ever-increasing number of adults are found to be tuberculin negative.

Although conclusive statistical data are lacking, apparently the primary infection in the adult is predominantly an asymptomatic process. When

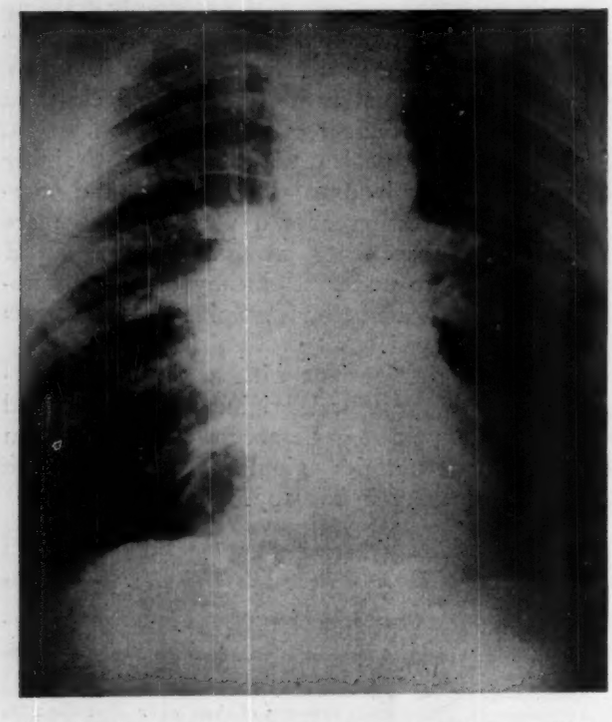

FIGURE 1. *Roentgenogram of the Chest, Showing Widened Mediastinum and Enlarged Hilar Lymph Nodes in Case I.*

lesions do appear in the lungs a few months after the conversion of a negative to a positive tuberculin test, they usually have the roentgenographic appearance of an ordinary, chronic type of adult or reinfection tuberculosis and follow a similar clinical evolution.[1-5]‡

Occasionally, in the adult there is a steady relentless progression of the disease until all the internal organs are infected and death ensues.

In 5000 consecutive autopsies at the Duke Hospital, Durham, North Carolina the diagnosis of disseminated tuberculosis was recorded 40 times in adult patients. A review of the protocols shows that a number were examples of chronic fibrocaseous tuberculosis with terminal dissemination. In other cases the initial infection may have been a primary one, but the course of the disease and even the autopsy findings were indistinguishable from those of the ordinary chronic "reinfection" type of tuberculosis. After these questionable cases had been discarded a residue of 20 remained in which the extent and character of the lymphatic involvement was characteristic of a primary infection. There were 11 males and 9 females in this group, varying in age from eighteen to sixty. Five patients were white, and 15 were Negroes.

The relative frequency of this type of tuberculosis is emphasized by the observations that in the same series of 5000 autopsies, there were only 20 lymphomas of the Hodgkin type, 4 cases of Addison's disease and 4 of hemachromatosis.

It must be confessed that the clinical diagnosis in these cases of progressive tuberculosis was usually incorrect. Except for the 5 that terminated with a tuberculous meningitis, only 1 case was correctly diagnosed ante mortem.

Perhaps the most important point to remember in making the diagnosis is that primary disseminated tuberculosis can occur in the adult as well as in the child. With the possibility of tuberculosis in mind, one then looks for local and general lymphatic involvement, including an enlargement of the spleen. Whereas the hilar lymph nodes are frequently enlarged, the lungs show little if any infection until the terminal stage, and the sputum, if present, is almost invariably negative for tubercle bacilli.

The tuberculin test is positive in the early weeks and months of the disease but may disappear as the patient becomes exhausted. The white-cell count may be either elevated or depressed, but there is almost always a specific decrease in the small lymphocytes.

Some of the variations in individual cases are illustrated in the following case reports.

CASE REPORTS

In the following case after a high, continuous fever with progressive enlargement of lymph nodes

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‡The clinical, roentgenographic and pathological aspects of experimental primary and reinfection tuberculosis in the rabbit have been studied in detail by Burke.[6, 7]

and spleen had developed, the patient died with minimal and terminal involvement of the lungs.

Case 1. A 51-year-old man noticed, over a period of 4 months, malaise, low-grade fever, anorexia, loss of weight and periodic chilly sensations without frank chills.

Physical examination showed a slight, general enlargement of all peripheral lymph nodes, and the ankles were moderately swollen and definitely red. No abnormalities were detected in the examination of the heart and lungs, but the spleen was palpable. A roentgenogram of the chest showed the widening of the mediastinum and enlargement of the hilar lymph nodes, with some diffuse peribronchial thickening (Fig. 1).

The temperature was 103°F., the pulse 104, and the respirations 22; the blood pressure was 126/70.

The red-cell count was 3,260,000, with a hemoglobin of 9 gm. (58 per cent), and the white-cell count 5640, with 60

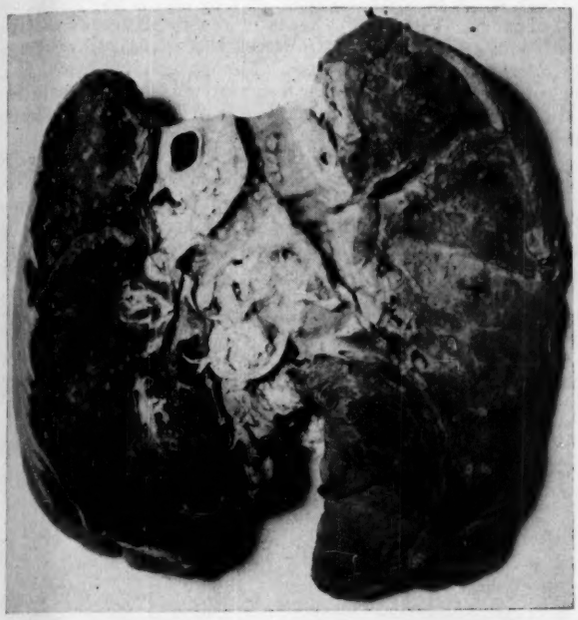

Figure 2. *Gross Specimen at Autopsy, Showing Caseous Lymph Nodes and Terminal Miliary Lesions in the Lungs (Case 1).*

per cent neutrophils, 12 per cent large lymphocytes, 24 per cent small lymphocytes and 4 per cent monocytes. Studies of the bone marrow showed a depression of all hemopoietic elements but no abnormal cells.

A tentative diagnosis of inoperable bronchiogenic carcinoma or lymphoma of the lymphosarcoma type was followed by a therapeutic trial of 1500 r.

The hilar infiltration increased slowly over a 10-week period. The temperature remained between 103 and 104°F. for 8 weeks and then became remittent for the last 2 weeks. A noma-like lesion appeared on the right cheek during the 5th week of hospitalization. Final examination of the blood on the day before death showed a red-cell count of 2,630,000, with a hemoglobin of 7 gm. (49 per cent), and a white-cell count of 2240, with 21 per cent segmented neutrophils, 33 per cent stab forms, 27 per cent juvenile forms, 12 per cent large lymphocytes and 6 per cent small lymphocytes.

Autopsy revealed a primary tuberculous pneumonia in the lower lobe of the right lung, caseation of the mediastinal lymph nodes (Fig. 2), generalized tuberculosis of the lungs, liver and spleen (Fig. 3), serofibrinous tuberculous pleurisy and secondary fusospirochetal gangrene of the right cheek.

In the following case the onset of primary progressive tuberculosis was insidious, with gradual involvement of the lymph nodes and spleen, suggesting the diagnosis of a lymphoma of the Hodgkin type.

Case 2. A 30-year-old man moved from a rural area into an industrial center. About 6 months later malaise, a low-grade fever and a slight generalized lymph-node enlargement developed. A roentgenogram of the chest showed a definite widening of the mediastinum, and a diagnosis of lymphoma of the Hodgkin type was made. A biopsy of a peripheral lymph node showed a granulomatous reaction and definite tubercle formation. The clinicians interpreted the finding of tubercles in the lymph node as incidental and reaffirmed the diagnosis of lymphoma.

The course of the disease, which was insidious in its beginning, now became more fulminating. There was marked malaise, anorexia, a spiking temperature and loss of weight. The patient became comatose and died 1 week later. The duration of the acute phase of the disease was a little over 8 weeks.

Autopsy showed the presence of large caseous hilar lymph nodes (Fig. 4), an enlarged, infected spleen, tuberculous meningitis and terminal miliary tuberculosis.

The following case, an example of a chronic, progressive, primary tuberculosis with destructive lesions of the vertebras, was incorrectly diagnosed as lymphoma, metastatic neoplasms or mycotic infection.

Case 3. A 40-year-old woman suddenly became ill 6 weeks before her first admission with chills, malaise and a temperature of 103 to 104°F. After penicillin therapy for 2 weeks and streptomycin for 1 week, the fever was reduced but not eliminated.

On admission in October, 1946, the patient apparently was chronically ill, with slight tenderness in the epigastrium

Figure 3. *Photograph of the Spleen in Case 1. The large white areas are tuberculous abscesses containing numerous tubercle bacilli.*

and the right upper quadrant. A roentgenogram of the chest showed a mass in the superior portion of the right hilus and another, smaller mass in the left hilar region.

Examination of the blood revealed a red-cell count of 3,650,000, with a hemoglobin of 10 gm. (69 per cent), and a white-cell count of 8500, with 75 per cent segmented neutrophils, 2 per cent eosinophils, 3 per cent monocytes and 20 per cent small lymphocytes. Studies of the bone marrow showed no abnormalities.

Small doses of x-ray, followed by large doses, were applied over the hilar masses. The masses slowly disappeared, and 3 months after admission she was discharged afebrile and apparently improved.

During the next 3 months at home some lymph nodes appeared in the neck but disappeared spontaneously. The discomfort in the right upper quadrant continued, and a new area of pain appeared beneath the lower third of the sternum.

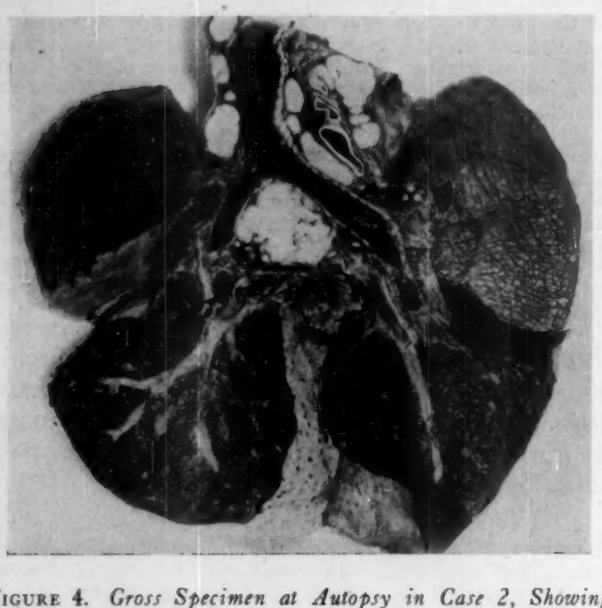

FIGURE 4. *Gross Specimen at Autopsy in Case 2, Showing Large Caseous Hilar and Peritracheal Lymph Nodes.*

Barium studies during the second admission in March, 1947, showed indentations in the esophagus suggestive of pressure by lymph nodes. She received 1250 r over this area and was discharged.

A low-grade fever persisted from March to July, and then a slight nonproductive cough, hoarseness and some difficulty in swallowing developed.

During the third admission in July, 1947, an x-ray film of the spine showed slight narrowing between the fifth and sixth cervical vertebras. An examination of the larynx revealed a paralysis of the right vocal cord. A tuberculin test was performed, for the first time, and found to be positive in a 1:1,000,000 dilution of old tuberculin. Desensitization to tuberculin beginning with a 1:100,000,000 dilution and progressing to 1 cc. of 1:1,000,000 was attempted.

The patient returned home, where she received 1 gm. of streptomycin daily for 6 weeks. Striking improvement occurred while the streptomycin was being taken and for a few weeks after it was discontinued. She became afebrile, felt quite cheerful and returned to work on a part-time schedule. By November, however, severe pains appeared in the mediastinal region, which required Demerol as often as three times a day.

During the fourth admission, between January 6 and 12, 1948, she seemed quite well and was afebrile, but x-ray study showed a destructive lesion with partial collapse of the fourth thoracic vertebra.

The fifth admission, between January 28 and February 7, was characterized by low-grade fever and bilateral pleuritic pain.

The final admission was on July 15. The patient gave a history of being almost well in March and April followed by fever and vertebral pain in May. Streptomycin treatment for 3 weeks produced a remission, but a relapse soon occurred and streptomycin now was ineffective although continued for an additional 4 weeks.

Physical examination showed the patient to be quite ill, and the abdomen was distended and tympanitic. The diaphragm was definitely elevated on the right, and films of the abdomen indicated that both liver and spleen were enlarged. She died on July 25, approximately 2 years after the beginning of her illness.

Autopsy revealed the residue of a primary tuberculous infection in the right upper lobe of the lung, scarred and fibrotic hilar lymph nodes and scarred and partially healed lymph nodes along the esophagus, and in the abdomen at the hilus of the liver. One of these lymph nodes was adherent to the stomach on one side and to the liver on the other. A rupture of this node into the stomach made a pathway for pyogenic organisms, which caused a large nontuberculous abscess in the liver. The destructive lesions in the bodies of the vertebras were tuberculous and not neoplastic.

In the following case, the primary infection was in the cecum, and the presenting symptom was an appendiceal abscess followed by evidence of aplastic anemia and low-grade intermittent fever. Finally, the development of round lesions in the lungs suggested the diagnosis of neoplasia with pulmonary metastasis.

CASE 4. A 60-year-old man was admitted to the hospital in February, 1940, with a mass in the right lower quadrant. A diagnosis of appendiceal abscess was made and confirmed by operation 2 months later. The patient recovered from the operation but became progressively more anemic and did not respond to iron, liver extracts or multiple blood transfusions.

A filling defect found in the region of the ileocecal valve by barium studies persisted throughout his illness.

The lungs were normal for the first 2 years, but during the last 2 years small, round discrete areas appeared in the chest films. Some of these areas decreased in size; others seemed to change in shape and outline, and new ones appeared from time to time.

The patient had fifteen admissions for aplastic anemia over a 4-year period and finally died in circulatory collapse.

At autopsy tuberculous ulcers were found in the colon. The mesenteric, retroperitoneal and mediastinal lymph nodes were caseous and contained tubercle bacilli. The spots in the lungs were tuberculous lesions (Fig. 5). The spleen was enlarged and contained miliary tubercles. The bone marrow from the humerus was essentially normal.

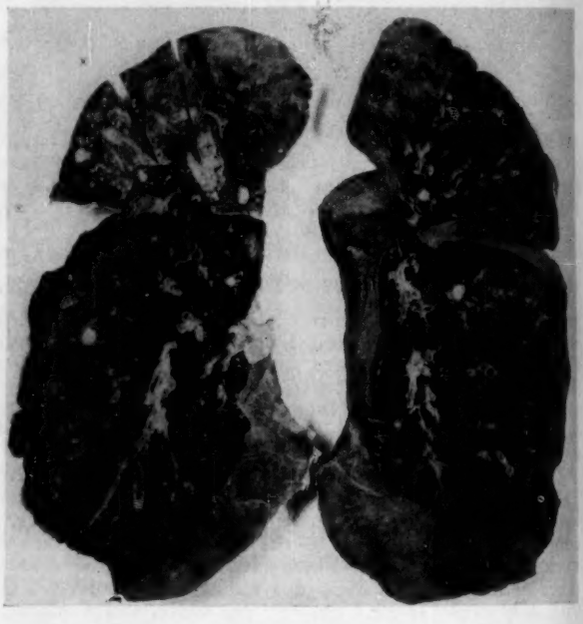

FIGURE 5. *Gross Specimen at Autopsy in Case 4, Showing Round Areas of Tuberculous Infiltration Scattered through the Lungs.*

Apparently, the primary infection was present in the cecum, and the hilar lymph nodes were not appreciably enlarged.

Differential Diagnosis

The difficulty in differentiating primary progressive tuberculosis and some types of lymphoma is obvious. Moreover, in the past decade, it has been found that certain types of mycotic infections duplicate the clinical picture of progressive tuberculosis almost exactly. Histoplasmosis, coccidioidomycosis, sporotrichosis and South American blastomycosis all have a progressive fatal form characterized by enlargement of the lymph nodes and spleen. They also frequently show destructive lesions of the bones.

Skin Tests

Twenty-five years ago tuberculin skin tests were rarely employed in internal medicine because almost the entire adult population was tuberculinized. At the present time, however, there are many areas in this country where less than 50 per cent of the adults have a positive skin test. Except in obviously moribund patients, a negative test to 1 mg. of old tuberculin or to the second strength dose of purified protein derivative practically eliminates the possibility of tuberculosis. One need not fear a false-negative test in the early stages of primary tuberculosis because the patient with primary tuberculosis does not develop symptoms until after the skin test becomes positive.

Skin tests with tuberculin-like antigens prepared from fungi are of definite but limited value in diagnosis. Positive skin tests develop quite regularly in persons who have had either a clinical or a subclinical infection with *Coccidioides immitis* or *Histoplasma capsulatum*; therefore, a negative skin test will eliminate the possibility of infection by these organisms unless the patient is in the terminal anergic phase of the disease. When concentrated antigens are injected into highly sensitized guinea pigs, cross reactions can be elicited with coccidioidin, histoplasmin and blastomycin.[8] This suggests that there is a minimal amount of a common antigen in all three fungi. In the doses commonly used for skin tests, persons with positive skin tests to coccidioidin do not give cross reactions with histoplasmin and blastomycin. However, *Blastomyces dermatitidis* and *H. capsulatum* share a larger amount of a common antigen.[9] Subjects who have had a subclinical infection with *H. capsulatum* usually react both to histoplasmin and to blastomycin, although in my experience the size of the reaction to blastomycin is always smaller and disappears completely if more dilute antigens are used for the test.

Complement Fixation

In contrast to the skin test, complement-fixing antibodies either do not appear or disappear shortly after a subclinical or mild primary clinical infection with *C. immitis*[10] and *H. capsulatum*.[11] However, in the progressive form of the disease the complement-fixing antibodies are regularly present, and the titer persists even when the anergic phase appears and the skin test becomes negative. Cross complement fixation is not observed between patients having coccidioidomycosis and histoplasmosis. Most patients, however, who fix complement to high titer with histoplasmin antigen also fix complement with the blastomycin antigen, but always at a lower titer.[11]

The complement-fixation test for tuberculosis is not reliable, but the new agglutination test introduced by Middlebrook and Dubos[12] may prove to be extremely useful in early diagnosis.

Biopsies

If an enlarged lymph node is accessible, a biopsy usually makes the differential diagnosis. The biopsy is particularly valuable in separating out the cases of sarcoidosis (Boeck's sarcoid) that may have been included with the lymphomas because the tuberculin test was negative.

The biopsy specimen should be cultured for tubercle bacilli and fungi. A culture is essential for the diagnosis of sporotrichosis, since the organisms are almost never seen in sections of human tissues.[13]

Cultures

All the yeast-like and mold-like fungi will grow on both 1 per cent dextrose agar and on blood agar at either room or incubator temperatures. Since growth may be very slow, the culture should be inspected every few days up to a maximum of thirty days.

Summary

With the rapidly increasing number of persons reaching maturity without becoming infected with tubercle bacilli, a larger number of adults will be found on the general medical wards with progressive primary tuberculosis. These cases resemble quite closely lymphoma of the Hodgkin type, progressive coccidioidomycosis and histoplasmosis, and, to a lesser extent, leukemia, aplastic anemia, metastatic neoplasm and sarcoidosis.

Before the discovery of promizole and streptomycin, the diagnosis of progressive primary tuberculosis was of academic interest only, but now, with a reasonably early diagnosis, some of these patients can be cured.

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HOSPITAL ADMINISTRATION AS A MEDICAL SPECIALTY*

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HOSPITAL administration as a medical specialty seems to be disappearing. The change may be more relative than actual, as able lay administrators become increasingly interested in an expanding profession, but few physicians, it seems, even consider the possibility of hospital administration as a career. What does the specialty offer? Should it be abandoned to trained laymen? In the search for answers to these questions, a brief review of the past history and the present status of hospitals and hospital administration may be of value.

One of the first hospitals of which there is record was founded by Justinian in Rome in 369 A.D. The first known hospital on this continent was established in Mexico by Cortez in 1524. A hundred and twenty years later the Hôtel Dieu was opened in Montreal. The first general hospital in the colonies was the Pennsylvania General Hospital, founded at Philadelphia in 1756. In 1811 the first general hospital in Massachusetts and the third in the United States was founded; it was opened in 1821 and still stands as a tribute to the Reverend John Bartlett and the two physicians, Drs. Charles Jackson and John C. Warren, who were instrumental in its establishment, as well as to the many who since then have added to its fame.

Since its beginnings in this country, the voluntary hospital has been rather an anomaly. It is founded and operated (at a loss) as a charity; it is supported by the time, skill and funds of physicians, individuals, businesses and lately by Community Chests; it is governed by a board of trustees, usually laymen; it often functions not only as a hospital but also as a health center for the area it serves. The hospital has often been referred to as "the physician's workshop." Could one imagine a manufacturer inviting workers into his plant to work for themselves with his equipment and his personnel? In a modified way this is the relation between the physician and at least the smaller hospitals. Although physicians care for service and private patients, the trustees have the final responsibility for everyone and everything in the hospital. They must hand down the policies by which the hospital operates and are, potentially at least, responsible for the adequate care of every patient, service and private. To execute the details of operation the trustees usually engage an administrator, who in turn supervises the operations of the hospital. He works with the staff to ensure adequate care of patients, to stimulate research and to co-ordinate the multiple aspects of the small city under his guidance. In addition, of course, he is concerned with purchasing and personnel, and may well have the added problems of an educational institution — at least a school of nursing, if not other more advanced medical-teaching programs.

How did this administrator come to be, and what is happening to him? In the early days, when hospitals were operated solely for the poor, a resident physician was usually engaged. His duties were to care for the patients and to administer the institution. It was preferable that he be married in order that his wife might serve as matron and housekeeper. As hospitals enlarged, both the operation of the institution and the care of the patient became much more complex. Gradually a division took place until the administrator was no longer directly responsible for the medical care of the patient. It is only in relatively recent times, however, that administrators have gathered together as a specialty group to establish uniform practices. The American Hospital Association held its fiftieth convention only last year. Thus, it is within the memory of many still living that hospital administration as a specialty and as a career has become known.

In 1933 a group of men meeting in Chicago formed the American College of Hospital Administrators, an organization to "establish high professional standards and to further the education of those in the hospital field." In the last sixteen years this organization has done much to advance the profession.

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Several universities have recently offered courses in hospital administration. The first successful course was estabiished by Dr. A. G. Bachmeyer at the University of Chicago. At present courses are also offered at Yale, Columbia, Washington, Minnesota, Northwestern and other universities. They consist of one year of didactic teaching followed by a year of internship in an approved hospital. Although the instruction is open to physicians, enrollment consists almost exclusively of laymen. Upon successful completion of the course, the student receives a master's degree in hospital administration. In contrast to these formal courses several hospitals have for many years offered to physicians apprenticeships in hospital administration; among these are the Peter Bent Brigham Hospital and the Massachusetts General Hospital.

When a man has completed his schooling or his apprenticeship, or both, he may be chosen by a board of trustees as director of a hospital. He then stands, as the American College of Hospital Administrators has put it, at the helm of the hospital; as others have put it, he is ground between the upper millstone of the trustees and the nether millstone of the staff. Neither description is completely accurate. Given a good board of trustees (and it never ceases to be impressive how loyal and understanding such a group of civic-minded citizens can be), he may, if he is a physician, "sit on the sidelines and watch the game," but he often has a better view than the man in the line. What are the disadvantages and the advantages of such a specialty for a physician? A few that come to mind are as follows:

Disadvantages:

He is not in business for himself and is subject to dismissal. As in any appointive position, his success (or failure) proceeds more by steps than by the gradual change usual in active practice. Every physician, however, has the same opportunities to succeed or to fail. To be sure, the administrator is working for a small group who have the power to hire and to fire, but his chances of proving his worth to a small group may well be greater than those of a physician to the general population of the city or town where he practices. Given a good board, and most hospitals have them, the hospital administrator will have every chance to show his capabilities and to grow in his chosen specialty. Should his situation for any reason become intolerable, he can usually effect a change without the financial loss entailed in relocating a practice.

His income is limited compared to that of a physician in some other specialty. This is very true, but although the peak may not be so high, he will probably do at least as well in the early years. Taxes being what they are today, this is perhaps better. His income depends upon the wishes of his trustees as well as his ability; this may be a disadvantage.

He must adjust himself to the personalities of trustees, staff, personnel and patients. At times these adjustments may be very difficult, but do not physicians have all of them to some degree, no matter what phase of medicine they choose?

He must operate a business. This is probably one of the greatest (if not the greatest) drawbacks for a physician. Most doctors go into medicine, in part at least, because they are idealists and rather shun the business side of life. The administrator must operate a big business — one of the largest in his community. He must operate it as economically as possible, and yet never with thought of profit. If he should operate in the black, he must give thought at once to a reduction in rates, for profit is not a purpose of a voluntary hospital. The multiple, complex problems of staff and personnel relations, wage schedules, purchasing, maintenance and all the others are with him constantly. To be happy in hospital administration a physician must enjoy business life to a certain extent.

He sits on the sidelines and watches the game being played. This, also, is one of the greatest disadvantages. The administrator must be willing to give up active, personal care of patients. He must, although using his knowledge as background, defer to his chiefs of services in matters of medical opinion. This disadvantage is balanced to some considerable extent by the first of the advantages noted below.

Advantages

He has an instrumental share in an enterprise greater than is possible (except for rare instances) in practice. Although he sits on the sidelines he has, throughout his career, a voice in calling the plays, in directing the progress of medicine in the hospital with which he is associated. From the professional side the course that is taken by his hospital during his tenure of office is in his hands to a greater degree than it is in the hands of any other staff member. What he may lose in the individual care of the patient, he gains in the setting of broad, over-all policy.

Community responsibilities. As director of a hospital today the physician, perhaps even as much as the public-health officer, represents to his community the general field of health. He serves on committees and organizations; he speaks to groups. Since he is not in practice he can take a much more active part in this phase of community life without fear of being unethical. As health has joined food, clothing and shelter to become the fourth necessity of life, so it is increasingly important that the story of health services be properly presented to an interested

public. The hospital director is constantly called upon to perform this civic duty.

His income is steady. Although he will never amass a fortune—and few doctors do— he is assured of a regular income, regular vacations and often the benefits of sick leave and retirement. His income is in many ways more secure than that of his fellow physicians.

His contacts are pleasant. In this aspect he differs little from the practicing physician.

His hours of work are better than those of most physicians. He is better able to schedule his time and can usually expect to work a more or less regular week. Meetings, often in the evening, and on-call coverage may be somewhat confining, but these, too, can usually be scheduled. By and large the physician administrator sees more of his family than the physician in practice does.

He has counsel available should he need it. The help that the administrator has available from his staff is obvious; in addition, if his board of trustees is a broad, representative body, he can, if he chooses, call upon any of several members for assistance in problems ranging from finance through personnel to workmen's compensation insurance. He rarely needs to sail without guidance on uncharted seas. The degree to which he may do so usually depends upon the man himself.

Are physicians interested in the future of hospitals? They must be, for hospitals are so increasingly intimately connected with the practice of medicine that neither can stand alone. If doctors are vitally interested in the future of hospitals, must they not be equally interested in their operation? The administration of the hospitals in this country is being taken over more and more by able lay administrators. This is not because medical administrators are so poor, but because they are so few. If those with no prior medical experience are recognizing the opportunities of this profession, are physicians not derelict in their duty if they do not bring its opportunities before medical students, interns and residents?

Given other qualities that are equal, it seems logical that since a hospital's prime reason for existence is care of the sick, a man with a medical background should make a better hospital administrator than one without. In the interests of the future of hospitals, therefore, and in the interests of medicine as well, it behooves physicians to keep the opportunities of this too often forgotten specialty before themselves and before those who follow them. While recognizing the importance of having able laymen in the field of hospital administration, they should reverse the trend of decline of hospital administration as a specialty chosen by physicians. The first step in such a program is to present the specialty for consideration to medical students, interns and residents.

MEDICAL PROGRESS

VIRAL INFECTIONS CONTRACTED IN THE LABORATORY*

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THE increased interest in viral diseases in recent years, particularly in the field of laboratory diagnosis, has stimulated more and more laboratories to undertake work with these agents. Diagnostic procedures that formerly were to be found only in periodicals have now been collected in a single volume by Francis and others,[1] who present them in a manner for ready reference for the average worker in the diagnostic laboratory. The availability of antigens§ for use in the complement-fixation test makes it possible for any laboratory familiar with this technic to detect an increased antibody titer for a number of viral agents. Because work on viruses gives promise of continuing to expand rapidly, it seemed timely to call attention to the possibility of laboratory infection by reviewing cases that have occurred in various laboratories in the hope that such information would indicate where the greatest need for caution exists. Furthermore, recognition of the causes of such accidents, as far as they are known, may stimulate confidence on the part of those who would otherwise be discouraged from attempting such work.

A number of cases of laboratory infection have been reported in the literature. Early in our survey, however, it became apparent that numerous cases have been observed that have not been reported. Accordingly, an attempt was made to obtain information regarding such cases. The gratifying response to the inquiry on the part of various investigators in this field has added considerable information.||

No exhaustive attempt has been made to survey the situation regarding laboratory infection with organisms other than viruses, although it is well known that many such infections have occurred, particularly with the brucella group,[2, 3] with *Pasteurella tularensis* and *Past. pestis*,[4, 5] with *Bacillus anthracis*,[6] with the typhoid bacillus,[7] with *Malleomyces mallei*,[8-10] with leptospira,[11, 12] with the borrelia,[14] with *Treponema pallidum*,[15] with *Coccidioides immitis*,[16] and doubtless with the tubercle bacillus and numerous other micro-organisms.[17, 18]

The hazards involved in work with rickettsias have also been recognized. Virtually all laboratories working with typhus rickettsias have experienced infections among the personnel.[19-22] *Rickettsia prowazeki*[23] and *R. mooseri*[24, 25] have been responsible for such cases. Vaccination does not, apparently, entirely remove the risk of infection,[26, 27] but the disease in vaccinated persons tends to be milder[28-30] and the incidence of infection is decreased.[31] Laboratory infections with *R. tsutsugamushi* (*R. nipponica*),[32] *R. rickettsi* (*Dermacentroxenus rickettsi*),[33] *R. conori*[34] and *R. quintana*[35] have also been reported. The first known human infection with the agent of American Q fever occurred as a laboratory infection.[36] Other laboratory cases of Q fever have occurred in Australia,[37] in the Mediterranean area[38] and in this country.[39-41] Even the most recent addition to the Rickettsia group, *R. akari*, has been responsible for 2 cases of rickettsialpox in the laboratory.[42]

Cases of viral infection that are believed to have been contracted in the laboratory are summarized in the accompanying Table 1 and 2. Those accidentally acquired outside the laboratory, such as the cases of encephalitis among veterinarians reported by Meyer[155] and Sulkin[156] and the case of equine infectious anemia in a person who had had contact with infected horses,[157] together with the numerous cases of psittacosis[146, 158] among bird handlers, have not been included. In a few cases as indicated in the tables, there is some doubt that the infection was acquired in the laboratory, but the possibility seemed strong enough to warrant its inclusion. The etiology was proved in most of the cases by one or a combination of the following technics: isolation of the virus; demonstration of a significant rise in neutralizing or complement-fixing antibodies in blood samples obtained during convalescence as compared with those drawn during the early phase of the illness; or demonstration of a significant antibody titer in a single sample of serum in a person who presented a typical clinical course of the illness in question together with evidence of exposure to the viral agent. In cases in which this evidence was lacking, there was little doubt regarding the nature of the infection.

In all, 222 cases with 21 deaths have come to our attention. Of the numerous viral agents involved, 5 have accounted for over two thirds of the infections — namely, yellow fever, Rift Valley

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§At the present time a number of viral antigens for use in the complement-fixation test are available commercially.

||We are indebted to the many workers in the field who contributed the data that made this review possible.

TABLE 1. *Viral Infections Contracted in the Laboratory.*

VIRUS	NO. OF CASES	NO. OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD *days*	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
Western equine encephalomyelitis (cases have occurred during animal experiments in Sweden[43,44]; data concerning these experiments not yet available).	2*	1	Laboratory accidents; patients worked with virus of chick-embryo origin.	14 (1 case) 4 (2 cases)	No (2 cases) Not tested (1 case)	Yes (2 cases) Not tested (1 case)	Helwig,[45] Gold and Hampil[46] and Wright[47]
	1*	1	Unknown; patient worked with virus.	<10	Yes	Not tested	Fothergill et al.[48]
Eastern equine encephalomyelitis	1	0	Unknown; patient worked with virus of chick-embryo origin.	Unknown	Not tested	Yes	Olitsky and Morgan[49]
Venezuelan equine encephalomyelitis	4	0	Unknown; patients worked with virus.	Unknown	Yes (1 case) Not tested (2 cases)	Yes	Casals et al.[50] and Lennette[19]
	8	0	Dust from contaminated mouse cages	3–11	Yes (6 cases)	Yes	Lennette and Koprowski[51]
	2	0	Unknown; patients worked with virus of chick-embryo origin.	3–4	Yes (1 case)	Yes	Koprowski and Cox[52]
	2	0	Indirect contact, inhalation of infectious material probable route of infection	3–4	Yes	Yes	Koprowski and Cox[52]
Russian spring-summer encephalitis†	1	0	Unknown; patient worked with virus.	Unknown	No	Yes	Olitsky[54]
Louping-ill	6‡§	0	Unknown; patients worked with virus.	Unknown	Yes (1 case)	Yes	Rivers and Schwentker,[54] Wiebel[58] and Wesemeier[59]
B virus‖; ascending myelitis.	1	1	Bite of apparently normal monkey	6	Yes	Not tested	Sabin and Wright[61]
Lymphocytic choriomeningitis (cases have occurred during animal experiments in Sweden[43,44]; data concerning these experiments not yet available).	7¶	0	Unknown; patients worked with virus.	Unknown	Yes (1 case) No (2 cases) Not tested (4 cases)	Yes (5 cases) No (1 case) Not tested (1 case)	Armstrong and Hornibrook,[62] Armstrong,[63] Dalldorf,[64] Hammon[65] and Sulkin[66]
	3	0	Laboratory accidents during work with infected animal tissues	9 (1 case) 17 (1 case) 10 (1 case)	Yes (2 cases) Not tested (1 case)	Yes (3 cases)	Lepine and Sautter,[67] Hayes and Hartman[68] and Milzer[69,70]
	2	0	One case not definitely established as laboratory infection; contact with mouse colony contaminated by virus previously described by Traub[71,72] and closely related or immunologically identical with virus of acute lymphocytic choriomeningitis of Armstrong and Lillie.[73]	Unknown	Yes	Yes	Rivers and Scott,[74,75] and Shope[76]
	1	0	Infected monkey lice	6	Yes	Yes**	Milzer and Levinson[77]
	1	0	Patient handled infected mice	Unknown	Not tested	Yes	Yamarat[78]
	1	1	No known contact with virus	Unknown	Yes	Not tested	Smadel et al.[79] and Schroeder[80]
	1	1	Patient assisted at autopsy of fatal case reported by Smadel et al.[79]	8	Yes††	Not tested	Smadel et al.[79] and Schroeder[80]
Durand's disease (virus D)	1	0	Unknown; not definitely established as laboratory infection.	Unknown	Yes	Not tested	Durand[81]
	1	0	Unknown; patient worked with virus.	4 (?)	Yes	Yes	Findlay[82]
Poliomyelitis	3	2	Contact with infected human or animal tissues	>9 (1 case) 21 (1 case) Unknown (1 case)	Yes (2 cases) No (1 case)	No (1 case) Not tested (2 cases)	Sabin and Ward,[83] Wenner and Paul[84] and Gear[85]
Mengo encephalomyelitis	1	0	Unknown; patient worked with virus.	5–8 (?)	Yes	Yes	Dick et al.[86]
Newcastle disease	2	0	Laboratory accidents during handling of infected allantoic fluid	1	Yes	Yes (1 case) No (1 case)	Burnet[87] and Anderson[88]
	3	0	Patients worked with virus of chick-embryo origin	1 (1 case) Unknown (2 cases)	Not tested	Yes (1 case) Not tested (2 cases)	Beard,[89] Shimkin[90] and Howitt et al.[91]
	1	0	Unknown	1	Yes	No	Anderson[88]
	5	0	Unknown; patients did not work with virus; possible aerogenic transmission.	Unknown	Not tested	Yes	Howitt et al.[91]
Yellow fever	21	2	Contact with infectious monkey blood or tissue	Unknown (18 cases) 10(?)(2 cases) 3 (1 case)	Yes (16 cases) No (4 cases) No data (1 case)	Yes (7 cases) No (13 cases) No data (1 case)	Berry and Kitchen,[92] Low and Fairly,[93] Jungmann,[94] Hindle,[95,96] Snijders,[97] Kuczynski,[98] Kuczynski and Hohenadel,[99] Burke and Davis,[100] and Rockefeller Foundation[92,101]
	3	2	Bite of experimentally infected mosquitoes	Unknown	Yes (1 case) No (2 cases)	Yes (1 case) No (2 cases)	None,[102] Burke and Davis,[100] Rockefeller Foundation[92]

TABLE 1 (*Continued*).

VIRUS	NO. OF CASES	NO. OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
				days			
Yellow fever	7	0	Handling of infected laboratory animals	Unknown (6 cases) 2 (1 case)	Yes (4 cases) No (3 cases)	Yes (6 cases) No (1 case)	Theiler,[103] Berry and Kitchen,[92] Low and Fairly,[88] Dinger,[104] and Dinger et al.[105]
	2	1	Handling of infectious human blood	10	Yes (1 case) No (1 case)	Yes (1 case) Not tested (1 case)	Low and Fairly[88]
	1	1	Autopsy on yellow-fever patient	No data	Not tested	Not tested	None[106]
	1	0	Unknown,	Unknown	No	No	Rockefeller Foundation[93]
Dengue fever	1	0	Contamination of conjunctival sac with human virus	10	No	Yes	Melnick et al.[107] and Sabin[108]
Rift Valley fever	3‡‡	0	Patients performed autopsies on infected lambs	5–6	Yes (2 cases) No (1 case)	Yes	Findlay[110]
	15§§	1||||	Unknown; patients worked with virus	Unknown (12 cases) 6 (1 case) 4 (1 case) 7 (1 case)	Yes (14 cases) No (1 case)	Yes (12 cases) Not tested (3 cases)	Schwentker and Rivers,[111] Kitchen,[112] Francis and Magill,[113] Magill,[114] Sabin and Blumberg[115] and Smithburn[116]
	5	0	Unknown; 1 case not definitely established as laboratory infection.	Unknown	Yes (1 case) Not tested (4 cases)	Not tested	Daubney et al.,[117] Francis and Magill[113] and Magill[114]
	1	0	Contact with infected animals	Unknown	Yes	Yes	Smithburn[116]
Colorado tick fever	1¶¶	0	Laboratory accident; patient handled infected mouse brain.	7	Not tested	Yes	Koprowski[118,119]
Mumps	1	0	Laboratory accident — contamination of mouth with infected monkey parotid gland	12	Not tested	Yes***	Enders et al.[121]
	1	0	Patient handled infectious saliva[2]	Unknown	Yes	No	Levaditi et al.[122]
	1	0	Sneezing of chimpanzee during attempt to inoculate intranasally with oral washings from patients	10–15	Yes	Not tested	Lepine[94]
Influenza	1	0	Laboratory accident — contamination of mouth by suction†	1½	Yes	Yes	Dinger[104]
	4	0	Animals experimentally infected with virus	Unknown (2 cases) <2 (2 cases)	Yes (3 cases) Not tested (1 case)	Yes (2 cases) Not tested (2 cases)	Smith and Stuart-Harris,[123] Laidlaw,[124] Sulkin[95] and Francis[125]
	1	0	Patient worked with virus of chick-embryo origin	3	Not tested	Not tested	Lacorte[126]
	1	0	Patient worked with throat washings from infected patients; not definitely established as laboratory infection.	<5 (?)	Not tested	Not tested	Krueger[127]
Vaccine virus	3	0	Patients handled large amounts of rabbit-adapted virus	Unknown	Not tested	Not tested	Beard[99]
Hepatitis (of viral origin?)	3	0	Unknown — probably exposure to contaminated serum; not definitely established as laboratory infection.	Unknown	Not tested	Not tested	Shaughnessy,[128] Hampil[129] and Stokes[130]
	1	0	Not definitely established as laboratory infection; patient handled infected stools from infected patients.	Unknown	Not tested	Not tested	Lepine[94]
German measles	1	0	Unknown — handling of throat washings and sputum from patient with German measles	<14	Not tested	Not tested	Sigel[131]
Viral diarrhea	1	0	Laboratory accident — contamination of mouth with corneal suspension	3	Yes	Yes	Dodd[132]

*Employed in the production of vaccine.

†Data not available regarding laboratory infections, including fatal cases, that occurred in Russia.[58]

‡One of these cases was reported by Critchley to Rivers and Schwentker[55] in a personal communication.

§Serum from one of these patients subsequently gave positive complement-fixation and neutralization tests with the Russian spring-summer encephalitis virus.[56,57]

||Only 2 other human cases (both of which were fatal) have been recorded (Olitsky and Casals[66]).

¶One of these cases was reported by Plotz to Armstrong[63] in a personal communication.

**Antibodies still present nine years after infection (Milzer[70]).

††The virus was also isolated by Dr. Muckenfuss, of the New York City Department of Health, and by Dr. Armstrong, of the National Institute of Health.

‡‡Neutralizing antibodies could be demonstrated in the serum of these patients four or five years after infection (Findlay[109]).

§§One of these cases was reported by Findlay to Kitchen.[112]

||||Patient died from pulmonary embolism following thrombophlebitis after convalescence seemed assured.

¶¶This patient also had laboratory infections with the viruses of yellow fever[92] and Rift Valley fever.[112]

***Skin test was positive two months after onset of illness (Enders et al.[120]).

fever, psittacosis, Venezuelan equine encephalomyelitis and lymphocytic choriomeningitis. The laboratory infections with yellow-fever virus have previously been reviewed by Berry and Kitchen.[92] It is of interest to note that, to our knowledge, no cases of laboratory-acquired yellow fever have occurred since introduction of vaccination. Also, it has been suggested that the use of the lyophile process for drying of infectious material may have contributed to the eradication of this danger.[159] This provides an excellent illustration of the possible elimination of a hazard by improved technic.

Recently, other workers[160, 161] suggested improved procedures designed to remove the risk involved in the preparation of complement-fixing antigens.

The 24 cases of infection with Rift Valley fever virus point to the high infectivity of this virus, but none of the cases observed by Smithburn[116] were severe. Death in the case reported by Schwentker and Rivers[111] occurred after recovery from the initial illness and was due to pulmonary embolism. Although many cases of ocular infection with vaccinia virus, usually associated with vaccination, have been reported, this infection rarely occurs as a laboratory accident in the course of preparation or experimental use of the virus.[162] The 3 cases of vaccinia observed by Beard[89] occurred in persons handling large amounts of highly concentrated rabbit-adapted virus.

In several cases a virus disease was first recognized among laboratory personnel.* The 6 cases of infection with louping-ill virus were the only known human cases until 2 naturally acquired cases were reported in 1948.[164] The first infections with the Newcastle disease virus among human beings observed were laboratory infections involving the eyes.† Until the recent report by Howitt and her associates,[91] the only naturally occurring human infections with this virus were also eye infections. The laboratory infections reported by these investigators were influenzal in nature, whereas the cases acquired outside the laboratory involved the central nervous system.

The original source of the "D" virus isolated by Durand[81] in 1939 from his own blood during

TABLE 2. *Laboratory Infections due to Agents of the Psittacosis-Lymphogranuloma-Venereum (Chlamydozoaceae*) Group.*

VIRUS	NO. OF CASES	NO. OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHOR
				days			
Psittacosis†	9	0	Laboratory accidents during work with virus	Unknown (3 cases) 7–14(6 cases)	Yes (7 cases) No data (2 cases)	Yes (7 cases) No data (2 cases)	Rosebury et al.[134] and Meyer[135]
	16‡	2	Patients handled or autopsied infected or possibly infected birds	Unknown (3 cases) 14(?)(1 case) 10–14(1 case) 7–10(2 cases) No data (9 cases)	No data (11 cases) Yes (2 cases) Not tested (3 cases)	Yes (4 cases) No data (9 cases) Not tested (3 cases)	Meyer,[135] Lepine,[94] McCoy[13, 136] and Moltke[137]
	14‡	0	Exposure to aerogenic transmission	Unknown (14 cases)	Yes (2 cases) No data (4 cases) Not tested (8 cases)	Yes (6 cases) Not tested (8 cases)	Meyer,[135] Meyer and Eddie[138] and McCoy[13, 136]
	16§	5	Unknown; patients worked with virus.	6 (1 case) 8 (1 case) No data (3 cases) Unknown (10 cases) <15(1 case)	Yes (4 cases) No data (11 cases) Not tested (1 case)	Yes (1 case) No data (12 cases) Not tested (3 cases)	None,[140] Rivers et al.[141] Meyer,[135] Canti,[142] Pfaffenberg,[143] Buchanan[144] and Gilbert[145]
	11	0	Unknown	No data (11 cases)	Yes (1 case) No data (10 cases)	No data (11 cases)	Roubakine,[146] Haagen and Krückeberg[147] and Sturdee and Scott[148]
Lymphogranuloma venereum	3	0	Unknown; patients worked with infected mice or chick-embryo and handled contaminated glassware.	Unknown	Not tested	Yes	Harrop et al.[149] and Shaffer and Rake[150]
	2	0	Unknown; patients worked in laboratory where virus was studied.	Unknown	Yes (1 case) No data (1 case)	Yes	Oliphant et al.[151] and Shaffer and Rake[150]
Atypical pneumonia	5	0	Unknown; patients worked with virus	4–8 (1 case) Unknown (4 cases)	Yes (4 cases) Not tested (1 case)	Yes (3 cases) Not tested (2 cases)	Beck and Eaton,[152] Meiklejohn et al.,[153] Svensgard[43] and Bodily[154]

*Family name recommended by Breed et al.[133]

†Numerous infections have occurred among dealers in birds.

‡The disease developed in 44 per cent of the personnel of a research laboratory in one building at the National Institute of Health.

§Rivers et al.[139] refer to infections that occurred in the laboratory of Dr. Krumwiede (New York City Department of Health); no details were given.

*The first definite human infections with the virus of Aujeszky's disease (pseudorabies) were 2 cases of laboratory infection.[163] The virus was recovered from the blood in 1 case.

†Freymann and Bang[165] have reported 3 additional cases of conjunctivitis due to the virus of Newcastle disease in laboratory workers. The virus was isolated from 2 of these patients, and antibodies were demonstrated in all 3.

a febrile illness is unknown. This agent, which was responsible for a single proved laboratory infection,[82] has not been encountered in recent years.

The summary presented in the tables shows that the exact mode of infection in many cases is unknown, recognized accidents accounting for only 27 of the cases. The fatal case of encephalomyelitis reported by Helwig[45] resulted when chick-embryo virus was thrown out of a centrifuge. The accidental splashing on the face of material from infected eggs was responsible for another case of encephalomyelitis[46] and for 2 cases of infection with the virus of Newcastle disease.[87, 88] Three of the cases of lymphocytic choriomeningitis were associated with known accidents. In one,[67] a piece of glass flew into a worker's eye while infected guinea-pig organs were being ground in a mortar; in another[68] a celluloid tube containing the virus was flamed; and in the third[69] the skin of the leg was accidentally punctured with a needle containing infectious material. The circumstances leading to a case of infection with psittacosis virus were carefully reconstructed by Rosebury and his associates[134] to show how a leaking ampoule containing a suspension of yolk-sac virus had contaminated the worker's hand and surrounding atmosphere. In the single case of B virus infection[61] the worker was bitten on the finger by an apparently normal monkey. The bites of experimentally infected mosquitoes were thought to be responsible for 3 of the laboratory infections with yellow-fever virus.[92, 100, 102] Contamination of the mouth by suction, a common laboratory accident, accounted for 1 case of influenza,[104] 1 case of mumps,[121] and 1 case of viral diarrhea.[132] These instances illustrate the manner in which such accidents can occur, and suggest the nature of the precautions that should be taken by the laboratory worker handling infectious material.

The cases of infection among laboratory personnel apparently contracted during the handling of infected chick embryos attest to the potential infectiousness of such material. Chick-embryo virus was thought to be the source of infection in 2 cases of Western equine encephalomyelitis,[45, 46] in 4 cases of infection with Venezuelan equine encephalomyelitis virus[52] and in the 1 case of Eastern equine encephalomyelitis.[49] Among the cases of psittacosis, of particular interest is a patient who had handled infected birds and mice for four years without infection but who became ill with proved psittacosis eight days after working with a suspension of virus from chick membranes.[140] The single case of meningopneumonitis-virus infection occurred in a person who had been using chick embryos for complement-fixation tests.[153] Seven cases of conjunctivitis due to Newcastle virus resulted from handling of infected chick-embryo fluids although Shimkin[90] referred to similar cases among kitchen workers handling food. Three cases of laboratory infection with the agent of lymphogranuloma venereum occurred among persons working with infected chick embryos.[149] One factor that contributes to the danger in handling infected embryonated egg tissues may be the high concentration of virus in such material.[166]

Several incidents show that a virus may retain its infectiousness for man even after many passages through animals. The strain of virus of Venezuelan equine encephalomyelitis responsible for the 8 infections reported by Lennette and Koprowski[51] had been passed through mice about fifty times. The virus responsible for a case of Rift Valley fever had been through four hundred mouse passages,[112] and another case at least three hundred mouse passages.[115] The laboratory case of yellow fever reported by Theiler[103] was probably caused by mouse-adapted virus in the thirty-second passage. Influenza virus recovered from the person who contracted the disease from infected ferrets was pneumotropic when transferred back to the ferret.[123] The alteration of the virus during animal passage, in this case, had not destroyed its infectiousness for man. Burnet and Bull[167] on the other hand, found that passage of influenza virus through chick embryos rendered it noninfectious on intranasal instillation in man. Repeated passage of many viral agents in chick-embryo tissues may result in decreased virulence for the natural host.[168, 169] In each of the 3 cases of poliomyelitis acquired in the laboratory the patient had been exposed to recently isolated strains.[83-85] During the two decades following the isolation of this virus the majority of work on experimental poliomyelitis was carried out with strains that were well established in the monkey; in recent years, however, many investigators have attempted isolation of the virus from the patient. Coincidentally, the laboratory infection reported by Sabin and Ward[83] in 1941 is the first recorded case of infection as a result of exposure to the virus in the laboratory. A second case of accidental infection with the virus was reported by Wenner and Paul[84] in 1947, and more recently, we were advised of a third case by Gear.[85] In each case the patient had been exposed to strains of poliomyelitis virus recently isolated from human cases. For this reason workers in the field are cautioned to observe the greatest care in handling tissue or excreta of human subjects and in working with monkeys infected with this agent.

An analysis of the circumstances leading to certain of the laboratory infections has provided important information regarding the transmission of these diseases. Since contaminated dust from mouse cages was apparently responsible for the 8 infections with the virus of Venezuelan equine encephalomyelitis reported by Lennette and Koprowski,[51] it seems likely that infection was by the respiratory route. Additional evidence for this possible route of infection is the fact that the virus was recovered from the nasopharyngeal washings

of 1 of the patients studied by Casals and his associates[50] and from 1 of the patients of Koprowski and Cox.[82] The possibility of direct transmission of the equine-encephalomyelitis viruses suggested by these observations is of interest in connection with the evidence for insect and other ectoparasite vectors in these diseases.[170-173]

In addition to these cases of recognized illness, there have been an unknown number of inapparent infections as shown by the acquisition of antibodies by numerous laboratory workers. For example, Olitsky and Morgan[49] found protective antibodies for Eastern equine encephalomyelitis virus in the blood of 1 out of 6 laboratory workers who had handled the virus for several years. To account for this finding, they suggest the possibility of viremia without invasion of the central nervous system. Another case of antibodies for the same virus in a laboratory worker without recognized illness was recorded by Wright.[47] Beard[89] observed 2 inapparent infections with the virus of Eastern equine encephalomyelitis and 1 with the Western equine virus. Seven persons who had worked with the virus of Venezuelan equine encephalomyelitis, 1 who had bottled formalin-treated vaccine and 1 who had performed postmortem examinations on horses dying of encephalitis showed neutralizing antibodies for this virus. Only the last had an illness that was recognized as probable encephalitis. The serum from 6 persons residing in the same locality but who had no laboratory contact with the virus showed no mouse protection.[174] A number of subclinical infections with the Western equine encephalomyelitis virus evidenced by positive neutralization tests occurred among workers producing large amounts of vaccine of chick-embryo origin.[175] Neutralizing antibodies for the virus of St. Louis encephalitis have appeared in the blood of a person who worked with this virus intermittently for seven years.[70] In this laboratory the development of neutralizing antibodies for equine encephalomyelitis virus has been observed in a person who worked with the virus without clinical signs of infection.[66]

A number of inapparent infections with the lymphocytic-choriomeningitis virus have been reported in animal caretakers.[76, 176, 177] At a time when 2 fatal laboratory infections with the virus of lymphocytic choriomeningitis occurred, a number of inapparent infections were detected by serologic study among other members of the laboratory personnel.[79, 80] An inapparent infection with the virus of louping ill occurred at the same time as 3 apparent laboratory infections.[54, 55] One person working with the virus of Ilhéus encephalitis developed a significantly high titer of neutralizing antibodies for this virus.[118, 178] An inapparent infection with mumps virus in a technician engaged in performing complement-fixation tests for mumps was reported by Enders and his associates,[121] and another case was observed at the Pasteur Institute at the same time that an overt infection occurred.[34] Two persons working with West Nile virus developed neutralizing antibodies without clinical symptoms.[179] A positive Frei test was recorded in a person a few months after he began working with the agent of lymphogranuloma venereum.[180] Four inapparent infections with the virus of Newcastle disease occurred at the time when 6 possible laboratory infections were observed.[91] One investigator contracted an inapparent infection with the virus of Russian spring-summer encephalitis while working with the agent.[181] In contrast to the above experiences, in some laboratories in which extensive virus work has been done no accidental viral infections have occurred, nor has there been evidence of inapparent infection.[34, 127, 182-184] Although work with the rabies virus is done in many laboratories, to our knowledge there are no recorded cases of laboratory infections other than those acquired by persons carrying out post-mortem examinations on naturally infected animals.

Summary

From published reports and from personal communications, 222 laboratory infections due to viruses are summarized. There were 21 deaths. The numerous viral agents involved include many that have been extensively studied, with the notable exception of rabies. Five viruses — namely those of psittacosis, yellow fever, Rift Valley fever, lymphocytic choriomeningitis and Venezuelan equine encephalomyelitis — accounted for over two thirds of the cases. An analysis of the probable source of these infections revealed that at least a third of the patients had become infected while handling infectious animals or tissues, 30 were presumed to have been exposed to a contaminated atmosphere, 13 had handled infectious material from patients, and 19 had worked with material from infected chick embryos. Known accidents were responsible for only 27 of the cases; these include a variety of situations, the most common involving the splashing of infectious material in the face or eyes. The first recognized cases of human infection with the viruses of louping ill and Newcastle disease were contracted in the laboratory. The data also reveal information regarding incubation periods and the route of infection in certain viral diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35311

PRESENTATION OF CASE

A thirty-seven-year-old machinist was admitted to the hospital because of sterility.

He had been married for a year and a half. His wife was thirty-nine years old and was said to be normal and fertile. One year before admission two examiners had reported no motile spermatozoa, and elsewhere he had been treated with a high-protein diet, thyroid and vitamin E. A third doctor gave him chorionic gonadotropic hormone. He admitted exposure to venereal disease but denied its presence by signs and symptoms. Intercourse was normal. The family history revealed the mother to be living; the father had died of coronary-artery disease. One brother and a sister were married and had children. There was no family history of twins. The patient had a middle-ear infection at the age of one and again at eleven, a mastoidectomy at age seven, circumcision at age thirteen and appendectomy at age thirty-four. At the age of thirty-five he was admitted to the hospital for acute abdominal and back pain. At that time his studies were essentially negative except for narrowing of the joint spaces between the eleventh and twelfth dorsal vertebras, which were fused, the abnormality being considered congenital. A gastrointestinal series was normal. Examination of the spine was negative. A retrograde pyelogram was suggestive of stone at the lower end of the left ureter. A bladder culture was negative, and the patient was discharged with the diagnosis of acute back strain. In the last two years he had felt logy, and the basal metabolic rate was said to be a "low normal."

Physical examination revealed a normal man of small stature who weighed 150 pounds and was 5 feet, 8 inches in height. The eyes, ears, nose and throat were normal, as were the heart and lungs. Examination of the abdomen was negative. The external genitalia were normal grossly on inspection and palpation. The prostate was normal in size and consistence. The examination of the prostatic secretion revealed no white cells.

The blood pressure was 120 systolic, 80 diastolic. The pulse was 80.

Examinations of the blood and urine were negative. A urine culture was negative. Two semen analyses revealed no spermatozoa. The follicle-stimulating-hormone qualitative test was negative and later positive for 6 mouse units for twenty-four hours. The 17 ketosteroids were 11.2 mg. per twenty-four hours and later 10.7 mg.

An attempt was made to catheterize the ejaculatory ducts, and the operator's note was as follows:

> The patient had a rather large flat verumontanum. Both ejaculatory ducts were visualized and catheterized for 1 cm. Good seminal vesiculograms could not be made because the dye exuded from the hole, which was beyond the amount of catheter inside the ejaculatory duct.

A testicular biopsy was reported as "No diagnostic abnormality recognized." An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FLETCHER H. COLBY: This is obviously a case of male sterility with azoospermia. There are so many factors that come into male sterility that it is difficult to discuss them all. At least we can say that male fertility is a rather delicately balanced affair. It is easily affected by many things, such as the patient's general condition, disturbances of the endocrine glands and temperature changes. A good many years ago Dr. Carl Moore, of Chicago, demonstrated the effect of heat on spermatogenesis. The temperature in the scrotum is believed to be lower than that in the inguinal canal or in the abdomen itself. He thought that this was why un-

descended testes have inadequate spermatogenesis. Dr. Moore's* studies were interesting and carefully controlled. He found that a fertile ram that had an oil silk bag tied over the scrotum soon lost active spermatogenesis. I saw an example of this a few years ago in a male sterility patient who had a small varicocele. In examining this patient I noticed that he wore a suspensory. I asked him how long he had worn it, and he replied three years, night and day. I suggested that instead of having the varicocele removed he take off the suspensory and send in another semen specimen. The first semen specimen showed 20,000,000 sperms per cubic centimeter. The next specimen, one month after the suspensory had been removed, showed 50,000,000, and he reported to me within the next month that his wife was pregnant.

The chief causes for azoospermia are occlusion of the seminal ducts from an inflammatory process, developmental defects, neoplasms of the genital tract and exposure to x-rays. Genital-tract infections as a cause of low fertility have never been adequately evaluated. We have all seen men who have a marked degree of infection in the prostate and seminal vesicle who have no difficulty in getting their wives pregnant. A recent patient with severe genital-tract tuberculosis, impregnated his wife in spite of the infection.

This patient gave no history of infection of the genital tract. The urine was sterile on culture, and the prostatic secretion was normal. Occlusion of the seminal ducts from inflammation, specific or nonspecific in character, was eliminated.

Neoplasms that may affect male fertility are new growths of the testes or spermatic cords or tumors within the prostatic urethra. There was no evidence of neoplasm in this patient. The presence of a papillary tumor of the prostatic urethra that could occlude the ejaculatory ducts may be dismissed by the attempt to catheterize the ejaculatory ducts. Failure to obtain seminal vesiculograms does not necessarily mean any abnormality of the ejaculatory ducts or seminal vesicles.

There is no history of exposure to x-rays.

Thus, we are brought to a defect in development as a cause for the azoospermia. Such a possibility is strengthened somewhat by the fact that a congenital defect of the vertebras was demonstrated by x-ray study, and where one congenital defect is present others are likely to exist. The congenital defects that may produce azoospermia are absence of the testes, imperfect testicular descent, imperfect spermatogenesis and congenital abnormalities of the epididymides and vasa deferentia. The testicular biopsy proved that both testes were normal, with active spermatogenesis. We are therefore left with the only remaining possibility: a congenital abnormality between the testes and the ejaculatory ducts. I should suppose the operation performed was to demonstrate this block in the seminal ducts, with the possibility, if conditions were favorable, of performing an epididymovasostomy.

This patient had been subjected to various forms of therapy in an attempt to improve his fertility, and illustrates the value of testicular biopsy in cases of azoospermia before treatment for male sterility is given.

Dr. Anne P. Forbes: Would the testicular biopsy be normal with long-standing obstruction due to congenital atresia?

Dr. Tracy B. Mallory: Can you answer that, Dr. Sniffen?

Dr. Ronald Sniffen: Yes; the biopsy could be normal.

Clinical Diagnosis

Congenital absence of vas deferens.

Dr. Colby's Diagnosis

Azoospermia due to congenital block in ducts.

Anatomical Diagnoses

Azoospermia.
Congenital absence of vas deferens.

Pathological Discussion

Dr. Fred A. Simmons: May I read my operative note?

Under spinal anesthesia a 3.8 cm. incision was made in the right scrotum, exposing the testis and epididymis. The testis was grossly normal. The epididymis was normal in the region of the globus major but rapidly thinned out into a fibrous band, and there was no evident globus minor or vas deferens. The spermatic cord was investigated thoroughly in various places, and there was nothing with any resemblance to a vas deferens. In this case fibrous substance disappeared into nothing at all, and no trace of a vas deferens could be found. The epididymis was normal in size. A biopsy was taken from the right testis. The same procedure was carried out on the left side.

*Moore, C. R. Physiology of testis and application of male sex hormone. *J. Urol.* 47:31-44, 1942.

My interest in presenting this case is to bring to the attention of the group the fact that the treatment this patient had before testicular biopsy was unnecessary because he was a normal man with obvious reason for infertility. The simplest way to make a diagnosis of infertility when there is no history of inflammatory disease is to take a biopsy from the testis and examine it microscopically. The specimen need not be any larger than the head of a hatpin. One of these patients, a man of twenty-nine, had perfectly normal testes and living spermatozoa in the epididymides, although he had obstruction.

We had 5 cases with epididymitis on the basis of gonorrhea, all with living spermatozoa in the epididymis. All but 1 had testicular biopsies reported as normal. I do not believe that fact is generally known in the literature, and often patients are deprived of having children.

Dr. Sniffen: In all our cases (about 50) of congenital or acquired defects in the excretory ducts the testicular biopsy has shown active spermatogenesis. One other condition that one might mention in a discussion of azoospermia is the complete absence of germ cells in an otherwise histologically normal testis. The cause of this abnormality is not known. It is apt to be associated with an abnormally high output of pituitary gonadotropins-

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CASE 35312

Presentation of Case

A seventy-two-year-old Italian man was admitted to the hospital because of a lump over the left breast.

Two years previous to admission the patient noticed a small, freely movable mass, the size of a bean, developing over the left breast just to the right of the nipple. It caused no pain or discomfort but continued growing. The patient denied any loss of weight or appetite.

Physical examination revealed a tumor mass, 6 by 8 by 2.5 cm., located just to the right of the left nipple between the fourth and sixth interspace. It was firm over the lateral part, softer over the medial and cystic in the center. The surface was rather smooth except for a nodule felt over the lateral part. It was adherent to the skin but not to the underlying muscle. The nipple was very slightly retracted, but there were no changes on the overlying skin. There were no enlarged axillary lymph nodes. Multiple warts were found over the back, and a small sebaceous cyst over the forehead. Examination of the lungs, heart and abdomen was negative.

The blood pressure was 155 systolic, 85 diastolic.

Urinalysis revealed no abnormalities. The hemoglobin was 11.5 gm. per 100 cc., and the white-cell count was 9800.

The x-ray examination of the chest revealed fibrocalcific scars in the upper-lung fields. Both upper lobes were reduced in size, and there was a partially calcified, 2-cm. lymph node at the right hilus. The left breast was enlarged and was particularly well shown in the lateral projection, in which view there was a suggestion of a small calcium fleck at the base.

On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Richard H. Wallace: May we see the x-ray films?

Dr. Stanley M. Wyman: The upper-lung fields show dense, fibrotic, partially calcified scars. The upper lobes are reduced in size, and the hili are elevated. There is a suggestion of a lymph node at the right hilus with some calcification within the node. The heart shadow is not remarkable. The aorta is probably calcified. The shadow of the left breast is well seen in the lateral view when viewed in a bright light and can be seen in the posteroanterior projection. The calcification described at its base probably represents calcified costal cartilage, rather than actual calcification in the tumor itself.

Dr. Wallace: This is really a rare case when we consider how unusual tumors in the male breast are in general. If one rules out senile mastitis or, better named, senile masoplasia and the enlargement of the male breast that follows hormone therapy, it is really very rare.

Carcinoma of the male breast comprises only about 1 per cent of all breast cancer. In the last 680 cases that Dr. Taylor and I reviewed from this hospital, there were only 4 cases of carcinoma of the male breast. However, this series included only cases with radical mastectomy. This particular case was certainly not the usual straight-

forward type of carcinoma — so it probably was something very unusual.

It was a tumor of two years' duration, starting as a small, movable, bean-sized mass that increased to the size of 6 by 8 cm., which is a fairly good-sized tumor, as one can see by the x-ray film. One interesting thing is the variation in the consistence of the tumor. It was hard and nodular on one side and soft on the other, with a cystic center, but there is no mention of transillumination, which might have been helpful, especially in the presence of fluid. Transillumination might well have shown the presence of dark, rather than light, clear fluid, which would be helpful. The dark fluid might be blood or old blood or broken-down tumor, which, of course, would influence one a little on deciding whether or not the tumor was malignant.

There was adherence to the skin. I am assuming that this was not inflammatory because of its duration and behavior and the absence of signs of inflammation. A tumor that involves the skin with adherence is practically always malignant. One confusing exception to that is fat necrosis, which can cause the picture that we generally consider characteristic, clinically, of carcinoma of the breast. There was no history of trauma in this case, and I do not believe that a tumor 6 by 8 cm. is very likely to have been — or, rather, I just do not believe that it could have been — fat necrosis. The nipple was slightly retracted, and, again, that suggests an invasive tumor. Of course, in the male the ductal portions are more likely to be involved than in the female. There were no palpable axillary nodes. That of course does not necessarily mean that this was benign. Some of the large tumors of the breast are found to be low-grade tumors and do not metastasize to the axilla. If it should be sarcoma, it is extremely rare to have sarcoma of the breast metastasize to the axilla.

It comes down to the question, Was this a malignant tumor or not? Perhaps there is some lead in this history, which to me might be misleading — that is, the sign of old tuberculosis within the chest. Whether or not this calcified fleck is in the tumor or not, as Dr. Wyman has said, is not definite by x-ray study. Could this have been tuberculosis with a broken-down area? I think it is extremely unlikely. I am not doing any more than considering the possibility. We do occasionally see calcium in breast tumors, usually as a result of long-standing tumor with hemorrhage either in the tumor or into a cystic area. It occurs occasionally in the long-standing papillary intraductal tumors that frequently bleed. Sometimes such a tumor will go on for a long time before it changes to become malignant, and old blood, either in the tumor from a small hemorrhage into the tumor or in the fluid, may cause calcification. Occasionally, a low-grade sarcoma of long standing will have areas of calcification. It certainly is an unusual tumor and, to my mind, it comes down to whether or not this was a carcinoma, probably arising in a papillary tumor, a fairly low-grade acinar tumor with degenerative areas or sarcoma of the breast.

Dr. Ira T. Nathanson: As Dr. Wallace pointed out, this is a very unusual type of tumor of the male breast. We have recently reviewed the records of a large number of male patients with breast disease. The large majority of lesions are benign. The physical and histologic characteristics in older men are very much the same as those commonly observed in boys at puberty. In fact, these lesions in the male are akin to the early development of the breast in the female. Clinically, the lesions are represented by firm, well localized, movable and disk-like masses of varying size in the subareolar area. Tenderness is a common feature. There is no evidence of skin attachment or invasion or retraction of the nipple. Histologic appearance is one of an increase and branching of the rudimentary duct systems, with accompanying fibrosis. Alveolar development is rare. The location of these lesions can be easily explained by the fact that the anlage of the breast is immediately beneath the nipple. These lesions in the male may be entirely unilateral or involve both breasts simultaneously or successively. The lesions in contrast to those arising as a result of disease elsewhere,* are considered an integral part of hormonal alterations occurring during puberty or at the climacteric. As a rule, these lesions regress spontaneously in both the young and the older males. Diagnosis is usually made without difficulty by those cognizant with the syndrome, and the patients are usually treated conservatively although careful observation is advised. If there is no regression after a reasonable period, excision is advised primarily for psychologic and

*Nathanson, I. T. Relationship of hormones to diseases of breast. *Surgery* **16**:108-140, 1944.

cosmetic reasons in the pubertal male. Cancer must be excluded by exploration in the older male if the process persists even in the absence of definite signs.

A study of almost 100 cases of proved cancer of the breast in the male has revealed that the diagnosis was made with few exceptions at the first examination. These tumors usually arise also in the subareolar area. But, in this case, there is evidence of invasion as manifested by dimpling or adherence to the skin, fixation to deeper structures and retraction of the nipple. This may occur early in the course of the disease since there is less breast tissue and usually less subcutaneous fat in the male. This characteristic may also permit easier accessibility of the tumor to routes of metastases.

Consequently, one would believe, as Dr. Wallace does, that the lesion under discussion was a malignant process because it presented two suggestive earmarks of cancer: skin adherence and retraction of the nipple. The prognosis of cancer in the male breast is less favorable than that in the female. This is probably due to the usually more advanced stage of the disease when the patient is first seen. Tenderness, a common feature of a benign process, is usually absent, and as a result the patient is frequently unconcerned until the diagnostic features of cancer are obvious. To reiterate, the lesion in this patient is rare, for most of the cancers in the male breast are of the more malignant type and invade and ulcerate early.

Clinical Diagnosis

Carcinoma of breast?

Dr. Wallace's Diagnosis

Carcinoma arising in intraductal papilloma.

Anatomical Diagnosis

Papillary adenocarcinoma of breast.

Pathological Discussion

Dr. Tracy B. Mallory: The specimen we received showed a partially solid, partially cystic tumor, which evidently had originally been an intraductal adenoma but had become slightly invasive at the periphery and was classified as a papillary adenocarcinoma of low-grade malignancy. It contained a great many flecks of calcium scattered throughout the tumor: small, round, concentric spheres, looking very much like corpora amylacea or the psammoma bodies that one sees in ovarian tumors. That is a distinctly unusual feature, and I do not offhand recall another breast tumor showing it. I believe, in view of various factors in the patient's condition, it was thought not wise to do a radical operation in this case, and a simple mastectomy was done.

Dr. Nathanson: The patient was discussed in the tumor clinic conference. A simple mastectomy was advised because it was thought to be a benign process. Once the final diagnosis became obvious, it was the consensus of the clinic, in conjunction with Dr. Castleman's opinion, that the patient would get by with a simple mastectomy. We would have done a radical resection had we suspected the diagnosis before operation. Do you agree, Dr. Taylor?

Dr. Grantley W. Taylor: Yes.

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THE EPIDEMIOLOGY OF MORALS

Time was when the public-health officer was verbally if not actually stoned for tacking the red scarlet-fever sign on the door — when the legal diagnosis of contagious disease and enforced quarantine was an un-American invasion of the family's and the family doctor's rights. The country has come a long way. Recently the United States Public Health Service has entered new and wider areas of investigation: for instance, community surveys of heart disease and diabetes, and latterly the incidence of marriage and divorce.

All pollsters are to be feared, even those bearing such fascinating gifts as Dr. Kinsey and his colleagues do. One cannot yet picture the hurried census taker or the eager district health worker inquiring after the waxing and waning of the nesting instinct in a harassed housewife at 10 o'clock in the morning. Nevertheless the interest of public-health authorities in the plain, uninterpreted figures on marriage and divorce means a beginning in the epidemiology of morals.

The Federal Security Agency's Public Health Service announces that both marriages and divorces have declined in the last two years, there being one third fewer divorces in 1948 than in the peak year 1946, when 610,000 divorces were granted. In 1948 there were one eighth fewer divorces than in 1947. The decline in divorce rate per 1000 in the three years is 4.3, 3.3 and 2.8. In 1946 there were 2,000,000 marriages, and in 1948 about 500,000 less. Marriage rates per 1000 in these three years were 16.4, 13.9 and 12.4.

There is no cause for encouragement in these figures on the brief postwar span. The heightened sense of so little time during the war doubtless intensified the urge to procreate, the appetite for the fullness of life experience or the search for emotional security in marriage. The special war situation in this respect has passed, and there are those who estimate that one in three marriages may still end in divorce. When statistics are reviewed over several decades,[1] it is found that both marriage and divorce have increased in relative frequency. The figures, moreover, do not indicate the effects of disrupted marriage on the children, the parents or society as a whole.

Most very young women are clear about the future. They plan to marry. As a young lady recently said to her father who was chiding her about a poor school report: "You don't need a diploma to get married." Most young men, it should be admitted, do not know what it is all about when they get married. The question, if not actually popped by the girl, is by pressures or contrivances put in the young man's mouth. In short, if he knows what he is doing, the young man is not in love. Marriages for sex alone soon pall and quickly fall apart. Marriages for children alone, after some years, find the mother without a job when her offspring are grown and in college or off on careers or marriages of their own, while the middle-aged father, aware of his failing powers, looks for a corn-haired sweetie to restore his confidence. How many friends for

whom one stood at the altar twenty-five years ago ask advice now because of a vague sense of cracking up and the windy melancholy, suggesting that one prescribe or approve a change of job, of locality and especially of wife! This was one of the factors that made the forty-five-year-olds so belligerent during the recent war. Contrariwise, not a few of the women approaching middle age, their tubes tied or the uterus removed on some pretext or other, have a sexual eagerness not easily satisfied by their disenchanted husbands. With all its rationalizations, divorce often is really a very banal affair of the glands and other monkey business. Divorce may be cunning or slick or smart, but it is not often intelligent. It is impulsive or instinctive; it may even result from an honest affair of the heart, but not of the educated or understanding heart.

Sigmund Freud[2] states that the id and the super ego struggle for the ego, which makes an uncertain compromise called neurosis or civilization. On this naturalistic basis there is reason for marriage in that it conserves the libido; the work of the world and human creativeness in this view are mere sublimations. In the gospel according to St. Paul, nineteen centuries ago, neurosis was well described and in closely similar terms: "For the flesh lusteth against the spirit and the spirit against the flesh: and these are contrary the one to the other: so that ye cannot do the things ye would" (*Galatians* **5**:17). The basis of this gospel is not naturalistic but is one of values not susceptible to proof by reason alone. The resolution of the neurosis is not by a life-long haggling in the economics of pleasure and pain but by the growing realization of individuality in devotion to another's good. The physiology of these opposite assumptions is identical. The one remains natural, the other adds that which makes man different from animals—the capacity to retain values and to pass them from generation to generation.

In this realm of values, human relations at their hoped-for best, and indeed man's relation to his universe, are represented in terms of family ties. An epidemiology of morals is a welcome barometer for the spiritual climate, apprising one of fair or foul weather ahead. At the moment the glass seems to be still falling in spite of the cheery figures from the Surgeon General. In these seas the general practitioner is more weatherwise. He should consult his own traditions and his best insights and appropriately admonish the voyagers committed to his care.

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2. Freud, S. *Civilization and Its Discontents.* 144 pp. New York: Jonathan Cape and Harrison Smith, 1930.

BRITISH–AMERICAN EXCHANGE FELLOWSHIPS IN CANCER RESEARCH

Of great interest is the recent announcement that the American Cancer Society, in conjunction with the British Empire Cancer Campaign, is offering British–American exchange fellowships in cancer research. The fellowships will provide specialized training for American investigators to study in Great Britain, where there are opportunities for study and research that are not generally available in this country. An equal number of young British scientists will be selected for specialized training in the United States.

The stipends are generous, and the fields of study offered suggest a sound approach to the problem of cancer in human beings. The annual stipend will be £1000 ($4020), with an allowance of $600 for travel to the site of the fellowship. The Committee on Growth of the National Research Council and the Empire Cancer Campaign must approve the institution where the applicant chooses to work and the persons under whose guidance he wishes to conduct his research, which should be applicable to problems of neoplastic growth in specialized scientific fields in which there are superior facilities in Great Britain.

The fellowships are open to United States citizens who possess the degree of doctor of medicine, doctor of philosophy or doctor of science, and are intended for young men and women entering a career in clinical medicine or basic research, as well as for more mature candidates who wish to extend their competence in these fields. Applicants must be able to show that they have the qualifications necessary to investigation in the fundamental sciences or in clinical medicine. Applications should contain reference to the institution in which the

proposed study is to be conducted, the person under whom the candidate desires to work, the problem to be investigated and the date on which he wishes to begin his research. Appointment to the staff of a university, with teaching duties, is permitted, provided it carries no additional salary and is acceptable to the two organizations sponsoring the fellowships, as well as to the Committee on Growth. Once accepted, the fellowship may not be vacated, nor the place of work changed within the period of tenure without the consent of all three organizations.

Applications may be submitted at any time to the Executive Secretary of the Committee on Growth, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

The fellowships should result in constructive progress in cancer research. It is to be expected that the applicants who benefit from the opportunity offered will also act as ambassadors of good will in the countries of their study.

WELFARE STATE

CONGRESS passed in June a record annual budget for public-health service that provided increases for mental health, cancer and heart research and aid to the various states. In addition a bill was introduced in the House, to which the medical profession certainly will not object, to raise the pay of all physicians, dentists and nurses in the Veterans Administration.

According to the terms of the Federal Security Agency's appropriations bill, 40 medical and 16 dental schools will receive $872,477 for training in cancer; 31 institutions, including the American Cancer Society and the American College of Surgeons will share $550,802 in special cancer-control-project grants; and 99 cancer-research projects will receive a total of $1,026,294.

Congress has further voted $100,000 for blue prints and specifications for the National Dental Research Institute to be built in Bethesda. (The American Dental Association favored $2,000,000 to start immediate construction.)

According to the details published in *Washington Report on the Medical Sciences* for June 27;

> National Heart Institute received a sizable $10,725,000 plus contractual authority of $5,350,000 for research and training grants. To National Cancer Institute went the record sum of $18,900,000 and, in addition, $6,000,000 in contractual authority. Another record figure of $11,612,000 was voted for mental health. And still another, $12,075,000 to National Institutes of Health, a large part of which will go for research, training, control and fellowship grants in noncategorized fields. Venereal disease activities get $16,000,000; for general assistance to the states, $16,600,000 is provided; communicable disease control functions receive $7,350,000; $167,000 is allocated for administering the Federal employe health program. For administration of the Hill–Burton hospital program, $1,200,000 was approved, obviating a drastic reduction in force which would have resulted if the Senate had yielded to the House figure of $1,000,000.

Without the aid of an adding machine the figures mentioned seem to total $108,528,573. For no particular reason at all, snatches of a conversation at the Mad Hatter's tea party come to mind:

"'And so these three little sisters' — (said the Dormouse) '— they were learning to draw, you know —'

"'What did they draw?' said Alice. . . .

"'Treacle,'* said the Dormouse. . . .

"'But I don't understand' (said Alice), 'Where did they draw the treacle from?'

"'You can draw water out of a water well,' said the Hatter; 'so I should think you could draw treacle out of a treacle-well — eh, stupid?'"

*Molasses.

A physician has opened his office on board an Ohio steamboat. . . . A mesmeric institution has been organized in the ancient city of Bristol, Eng., of which Earl Ducie is president. He is a decided believer in all kinds of moonshine.

Boston M. &. S. J., *August 1, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

KING — Francis B. King, M.D., of Derry, New Hampshire, died on July 10. He was in his forty-sixth year.

Dr. King received his degree from Tufts College Medical School in 1934. He was formerly a member of the staffs of Boston City and Boston Psychopathic hospitals and Harper Hospital, Detroit.

His widow, a daughter, a son, his mother and a brother survive.

(*Notices on page xv*)